Renal denervation restores autonomic imbalance and prevents atrial fibrillation in patients with hypertensive heart disease: A pilot study

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PhD Dissertation

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DECLARATION

By submitting this dissertation, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third-party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Marshall Jacobus Heradien

March 2020

"My heart and kidneys are fighting each other;

Call a truce to this civil war."

Psalm 25: 17

(Message Bible)

LIST OF ABBREVIATIONS

Medical terminology

ABPM	automated blood pressure monitoring/ monitor
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AF	atrial fibrillation
AHR	ambulatory heart rate
AHT	antihypertensive therapies
AI	autonomic imbalance
AT-II	angiotensin II
AV	Atrio-ventricular
BMI	body mass index
BMW	Balanced Middleweight Wire
CAD	coronary artery disease
CAT	Cardio-autonomic tone
CPAP	continuous positive airway pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EST	exercise stress test
HHD	hypertensive heart disease
HRR	heart rate recovery
ILR	implantable loop recorder
IST	increased sympathetic tone
IVSd	interventricular septal wall dimension during diastole (mm)
LA	left atrial
LAVI	left atrial volume index
LV	left ventricle/ left ventricular
LVEDD	left ventricular end-diastolic dimension (mm)
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
NSTEMI	non-ST-elevation myocardial infarction
PVI	pulmonary venous isolation
PWd	posterior ventricular wall dimension during diastole (mm)
QTc	corrected QT interval
RCTs	randomised controlled trials
RD	renal denervation
RHR	resting heart rate
SAF	subclinical atrial fibrillation
SBP	systolic blood pressure
SVES	supraventricular extrasystoles
TIA	transient ischemic attack

Mathematical/statistical/other abbreviations

2D	two-dimensional
6MFU	six months follow up
ANCOVA	analysis of covariance
BL	baseline
CI	confidence interval
HREC	Health Research Ethics Committee
OR	odds ratio
RR	risk ratio or relative risk
RTM	regression to the mean
SDNN	standard deviation of normal to normal R-R intervals

Units

bpm	beats per minute
IU	International Unit
mmHg	millimetre of mercury

PERSONAL REFLECTION

Professor Paul Brink introduced me to a "stepchild" in Cardiology: the autonomic nervous system and its central role in malignant cardiac arrhythmias. Our mentoring relationship and friendship started more than two decades ago. He taught me about sudden cardiac death the long QT syndrome and hypertrophic cardiomyopathy and connected me with world-famous researchers of whom Professor Peter Schwartz played a central role in developing our current thinking about autonomic nervous system modulation of cardiac arrhythmias.

I became an interventional cardiologist but remained interested in the autonomic nervous system and its effect on sudden cardiac death and atrial fibrillation. Renal denervation (RD) was introduced as a novel, minimally-invasive blood pressure-lowering procedure. In 2012, I approached the device company, Medtronic, with my idea that RD could potentially be used as an anti-fibrillatory tool, and after many refusal letters, they finally accepted my research proposal!

Trouble on the horizon

I was never interested in blood pressure lowering from a research perspective, especially after the disappointing results of SYMPLICITY HTN-3. This trial is considered a landmark trial which emphasized the power of a “sham” procedure. Although SYMPLICITY HTN-3 had technical limitations, it lead to the design of new catheters and three ongoing trials that demonstrated a modest reduction in blood pressure between 5-10mmHg. Nonetheless this was far less than the previous reports in unblinded controls without a sham procedure of a 30-mm drop in blood pressure and the “power of the placebo” is a major contribution from this trial.

Abandon ship?

Many concerned colleagues warned me that I was on a sinking ship and that I should consider changing my PhD. Paul Brink and my wife, Tania Heradien, encouraged me during the stormy seas that followed. Despite these challenges, I continued dreaming about the anti-arrhythmic effects of RD.

A silver lining behind the dark cloud?

The results of my study were quite surprising, unexpected (e.g. reduction in NSTEMI incidence) and sometimes, even disappointing. I console myself that other researchers will continue to challenge dogma and push scientific boundaries until they break! In this regard, I dedicate this work to the late Professor Bongani Mayosi, who was such a researcher.

Bongani Mayosi: 1967-2018

My heartfelt thanks to you for all your input and encouragement! Thank you also to the Hamilton Naki Trust for providing me with financial study support. Let us continue to live our lives by the Ubuntu principle and share knowledge freely to empower Africa and equip her children for the bright future that lies ahead.

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3. **My children**: Thanks for giving Dad time to embark on and finish this long journey!
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5. **My Mom**: who bought my first microscope with money that she saved for months!
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    - **Andre Saaiman** believed in me, when no-one else did. Without you, this study would not have materialised. Period. Thanks, Andre.
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ABSTRACT

BACKGROUND

Atrial fibrillation (AF) is associated with increased cardiovascular morbidity and mortality, but it is uncertain if catheter-based renal denervation (RD) can reduce AF in patients with hypertensive heart disease (HHD).

METHODS

Patients who were ≥ 55 years old, in sinus rhythm, taking ≥ 3 anti-hypertensive drugs including a diuretic, with echocardiogram-confirmed HHD and suspected coronary artery disease, were randomised to undergo RD or sham procedure. Patients with renal impairment, significant valvular heart disease and untreated thyroid disease were excluded. The primary endpoint, the first episode of subclinical AF (SAF) lasting ≥ 6 minutes, was detected using an implantable loop recorder which was scanned every six months. Six-month follow-up (6MFU) office systolic blood pressure (SBP), cardiovascular mortality and restoration of autonomic imbalance were secondary endpoints.

RESULTS

Eighty patients were randomised: 42 underwent RD and 38 a sham procedure. After an average follow-up of three years, fewer RD patients experienced SAF: 6 of 42 patients (14.3%) vs 15 of 38 (39.5%) sham patients (odds ratio (OR), 0.26; 95% CI, 0.1 to 0.71, p = 0.01). Fast AF (ventricular rate ≥ 100 bpm) occurred in 10 sham patients (26.3%) vs 1 RD patient (2.4%): OR, 14.64; 95% CI, 1.77 to 120.91; p = 0.002). The incidence of cardiovascular death was higher in the sham than RD group (6 of 38 (15.8%) vs 1 of 42 (2.4%): OR, 7.69; 95% CI, 0.88 to 67.12; p = 0.049). Non-ST elevation myocardial infarction (NSTEMI) incidence was lower in the RD than sham group (2.3% vs 18.4%: OR, 0.108; 95% CI, 0.01–0.92; p = 0.02). The 6MFU between-group SBP difference was not significant (−3.8 mmHg; p = 0.49). Resting and one-minute recovery heart rate did not differ between groups at 6MFU.

CONCLUSION

In patients with HHD, RD reduces subclinical and fast AF, NSTEMI and cardiovascular death independent of lowering blood pressure. RD was not associated with improvement of surrogate markers of autonomic imbalance.

CHAPTER 1

INTRODUCTION

This section focuses on the epidemiology and current treatment guidelines of hypertension. Non-adherence to oral anti-hypertensive drugs (AHD) limit their efficacy and should be excluded in every patient with so-called "resistant hypertension". Different AHD classes are discussed, focusing on sympathetic nervous system overactivity and its association with hypertensive heart disease (HHD) and paroxysmal atrial fibrillation (AF). Current AF management and its shortcomings, as well as the rationale why catheter-based renal denervation may be considered as alternative upstream therapy to prevent AF in patients with HHD are also discussed.

Hypertension epidemiology and target organ damage

Hypertension (HT) remains the most common and modifiable cardiovascular risk factor. In 2015, the global prevalence of HT, based on an office blood pressure of > 140/90 mmHg was estimated to be 1.13 billion.[1] Although the prevalence of HT is declining in high-income countries, an increased prevalence has been reported in lower-income Sub-Saharan and East-European countries.[2] Current data also indicate that the incidence of newly-diagnosed hypertension is increasing among young adults and both genders.[3] More than 60% of people aged > 60 years have hypertension.[4] South Africa has probably one of the highest prevalences of HT (77.9%) among older adults within low and middle-income countries.[5] Uncontrolled HT is associated with damage to target organs including the brain, eyes, heart and kidneys. Cardiac complications of uncontrolled HT include hypertensive heart disease (HH), coronary artery disease (CAD) and atrial fibrillation (AF).[6]

Current ESC/ESH guidelines for the treatment of hypertension

Current treatment guidelines recommend lifestyle changes as the first step in the management of arterial HT.[7] These include dietary adaptations such as salt reduction and increased fruit and vegetable intake. Increased physical activity, at least 30 minutes/day for most days of the week, also lowers blood pressure. Although these lifestyle changes can induce significant blood pressure lowering, they are often hard to maintain. A randomised controlled trial showed that motivated patients can maintain the blood pressure-lowering effect for up to 18 months, which could help to delay starting with anti-hypertensive treatment and of diabetes mellitus.[8] Frequently, however, most patients will need life-long drug therapy to reduce the risk associated with uncontrolled HT.

Non-adherence to anti-hypertensive therapies is the most common cause of uncontrolled HT. It is estimated that 50% of hypertensive patients will become non-adherent to their prescribed medicines within the first year of diagnosis.[9] One of major explanations for nonadherence to antihypertensive therapies is that patients are simply not compliant and not necessarily because of side effects but because they are not sufficiently symptomatic with hypertension until they get complications.

Several anti-hypertensive drug classes may be used, but 2018 ESC guidelines recommend that most patients should be treated with a **single-pill strategy** that contains at least two anti-hypertensive drugs of different classes.[7] Any combination is physiologically feasible, but angiotensin-converting enzyme (ACE) inhibitors should preferably not be combined with angiotensin receptor blockers because of the risk of irreversible renal failure, hyperkalaemia and failure of demonstrating improved survival.[10]

Types of anti-hypertensive drugs and their side effects

Diuretics are most commonly prescribed and are usually effective to lower blood pressure, but thiazide diuretic use is associated with hyperglycemia, hyperuricaemia, hypokalaemia and dyslipidaemia.[11] Recently an association with skin cancers was reported with thiazide diuretic use.[12] When compared to thiazide diuretics, thiazide-like agents, such as Indapamide, resulted in an additional 12% relative risk reduction (RRR) for cardiovascular events and a 21% additional RRR for heart failure.[13] These agents are also "metabolically neutral", implying that, unlike thiazides, they do not worsen the patient's lipid or diabetes profile. Thiazides are cheaper than thiazide-like agents and remain the preferred diuretic in resource-poor settings.

Renin-angiotensin system blockers are essentially vasodilators which are especially effective in non-African, hypertensive patients.[14] Angiotensin converting enzyme inhibitors (ACE-I) significantly lower the production of angiotensin II and raise nitric oxide levels via increased bradykinin levels.[15] This beneficial effect of ACE-inhibitors is sometimes associated with an intractable cough, which often leads to discontinuation of this valuable therapy. Angiotensin-receptor blockers (ARBs) produce much less cough and accordingly, associate with much less drug discontinuation than ACE-inhibitors.[16] In meta-analyses, however, ARB treatment could not demonstrate any cardiovascular mortality reduction (HR: 0.99, 95% CI: 0.94–1.04).[17] ACE-inhibitors on the other hand, reduced overall cardiovascular mortality by 10% (HR: 0.90, 95% CI: 0.84–0.97). Despite the statistically significant cardiovascular mortality benefit of ACE-I over ARBs, current ESC guidelines do not recommend one agent over the other. It is probably important here to mention that the ACEi trials were performed during an earlier time period when morbidity and mortality was higher.

Aldosterone antagonists prevent the reabsorption of sodium and water in the distal convoluted renal tubules. Spironolactone remains a valuable drug in the management of low-renin states and resistant hypertension, but treatment is associated with hyperkalaemia and gynaecomastia, which is less common with eplerenone.[18, 19] **Amiloride** is also a potassium-sparing diuretic with mild natriuretic and diuretic properties.[20] It selectively blocks sodium transport in the distal renal tubule which inhibits sodium-potassium exchange. Hyperkalaemia, nausea and vomiting, loss of appetite, muscle cramps and impotence are common side effects which may reduce adherence.

Non-dihydropyridine calcium channel blockers are a mainstay of blood pressure lowering therapy in many parts of the world. **Dihydropyridine calcium channel blockers** are also effective in the management of hypertension, but treatment is associated with ankle oedema, which may lead to non-adherence. This class of anti-hypertensive treatment is preferred in black hypertensive patients, but should preferably be avoided in patients with heart failure with a reduced ejection fraction (HFrEF). [21] **Hydralazine** is a vasodilator that reduces peripheral resistance by working directly on vascular smooth muscle cells. Reflex tachycardia with angina, gastro-intestinal side effects and drug-induced systemic lupus erythematosus may limit its use.[22]

Alpha-blockers (AB) are vasodilators and considered a valuable add-on anti-hypertensive therapy especially in males with benign prostate hyperplasia.[23] Unfortunately, AB treatment is associated with orthostatic hypotension which may increase the risk of falls and fractures in the elderly. **Beta blockers** are second line agents in the treatment of hypertension probably because they are associated with least LVH regression, more effort intolerance and male

impotence compared to other anti-hypertensive classes.[24] In the ASCOT trial, Atenolol, which is still used in the South African state sector, increased the risk to develop diabetes mellitus.[25] Despite these negative associations, BB remain important drugs in the treatment of patients with long QT syndrome, ischemic heart disease and heart failure.[26, 27]

Does sympathetic activity play a role in atrial fibrillation?

Several conditions are associated with increased sympathetic tone (IST) which plays a central role in the development of HHD. These include the metabolic syndrome (central obesity, hypertension, insulin resistance, dyslipidaemia and hypercoagulability), obstructive sleep apnoea, diabetes mellitus, emotional stress and depression.[28-30] HHD is characterised by left ventricular hypertrophy (LVH), diastolic dysfunction, increased left atrial pressure (LAP) and left atrial dilatation.[31] Increased LAP stretches the pulmonary veins and induces ectopic electrical foci that seldom upset normal sinus rhythm (Figure 1).

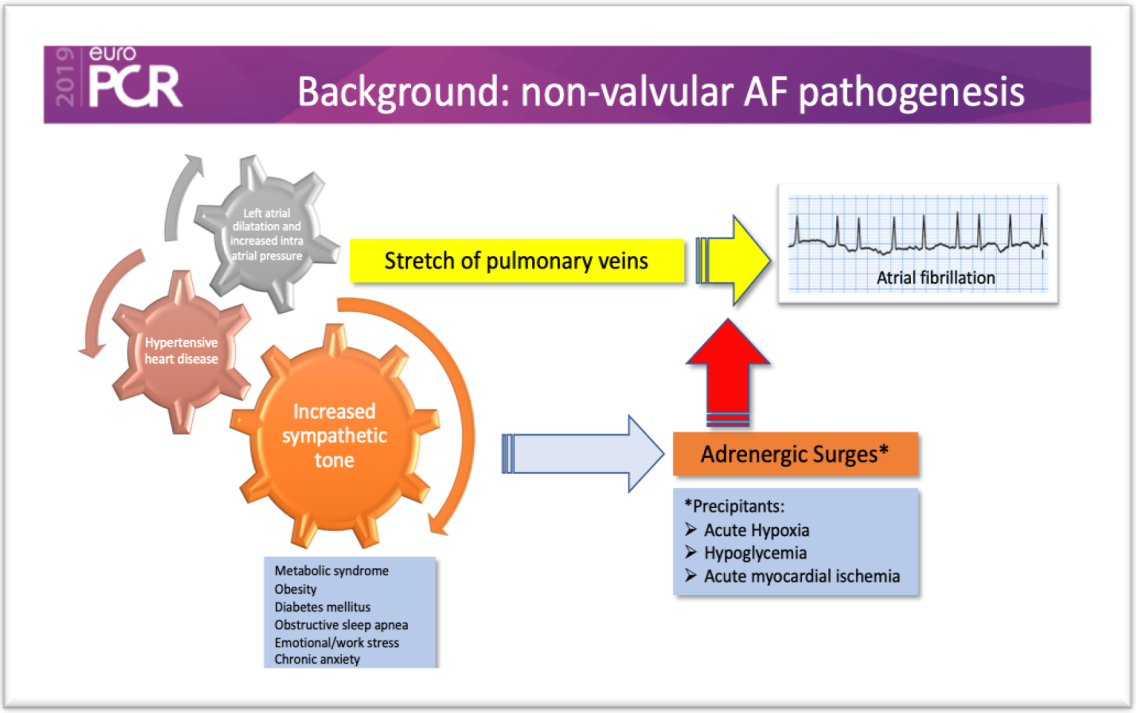


Figure 1. Increased sympathetic tone promotes the pathogenesis of non-valvular atrial fibrillation. Proposed mechanism of how increased sympathetic tone promotes the development of hypertensive heart disease, left atrial dilatation and stretching of the pulmonary veins. Adrenergic surges can precipitate subclinical and fast AF on this primed substrate. (Slide presented by the author at Euro PCR: Paris, France; 2019).

This situation may change, however, when the patient experiences a sudden surges of increased sympathetic tone which releases catecholamines on the primed substrate, the pulmonary venous ostia. Typical triggers of these events are hypoglycaemia, hypoxia and acute myocardial ischemia. Hypoglycaemia may be a side effect of administered insulin or first-generation sulfonylurea drugs. In the DEVOTE 3 trial, patients who experienced insulin-induced severe hypoglycaemia were at greater risk of death after the hypoglycaemic episode.[32] Hypoxia may be experienced by patients with obstructive sleep apnoea (OSA) and myocardial ischemia, which may be either acute or chronic, occur in patients with obstructive coronary artery disease. During these hyper-adrenergic events, short duration and fast AF occurs.[33] These short-lived episodes seldom cause symptoms, unless the patient has advanced left ventricular diastolic dysfunction. The association between symptomatic atrial fibrillation, obesity, and OSA appears to be strong: in anyone with nocturnal development of atrial fibrillation it should be considered and in patients undergoing radio-frequency ablation, screening for OSA is advisable.[34] It is also important to remember that the same risk factors which increase sympathetic tone can also increase arterial stiffness which in turn causes diastolic dysfunction and increased left atrial volume.[35] Furthermore, a large atrium is electrically unstable due to inhomogeneity in conduction and refractoriness.[36]

Atrial fibrillation: epidemiology, predisposing factors and pathogenesis

AF is the most prevalent sustained cardiac arrhythmia. Millions of people are affected worldwide and the prevalence increases with age.[37] Males are more frequently affected than females.[37] It is estimated that in the next decade, 14–17 million people in the European Union will be diagnosed with AF.[39] Non-valvular AF occurs more frequently in developed countries, probably because these populations have better access to health care, which facilitates

quicker diagnosis and associates with increased life expectancy. It is also well documented that there is a lower incident AF rate amongst black Americans and perhaps other black populations even though they have more left ventricular hypertrophy.[40]

This picture may be different in developing countries, however. An Ethiopian community-based, cross-sectional study recently reported a relatively high prevalence of AF of 4.3% in 634 adults screened with a 12 lead ECG, but AF prevalence data in Sub-Saharan Africa remain sparse, despite the relatively high prevalence of valvular heart disease.[41, 42] Conditions that are independently associated with AF include diabetes mellitus, obesity, ischemic heart disease, hypertension and aging (Figure 2).[43]

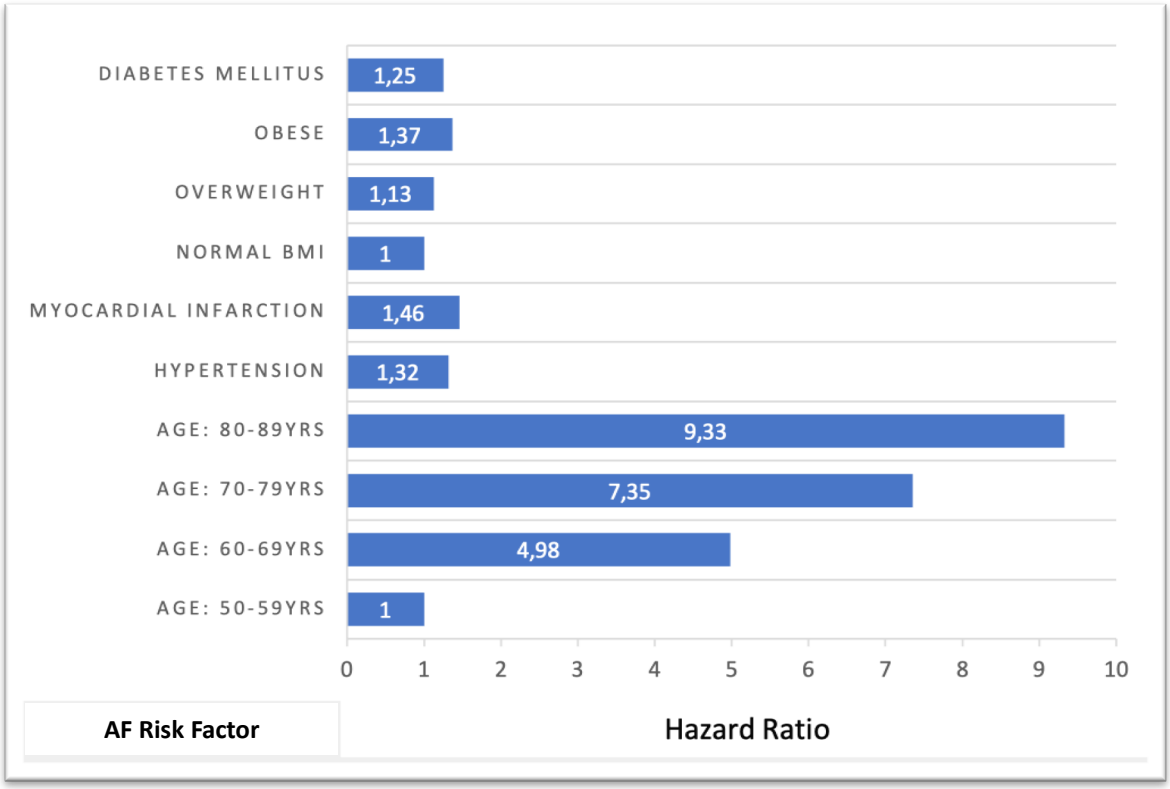


Figure 2. Hazard ratios of risk factors that are independently associated with non-valvular Atrial Fibrillation. Adapted from 2016 ESC guidelines on Atrial Fibrillation: www.escardio.org/guidelines.[43]

Young people (age < 60 years) with a normal BMI and no other cardiovascular risk factors do not have an increased risk to develop AF. Lone AF, also referred to as “vagal AF”, which may be genetically determined to some extent, occurs more frequently in younger than older patients. Octogenarians have the highest risk to develop AF (HR: 9.33; 95% CI: 6.68–13.0) and in patients with hypertension the risk to develop AF is increased by 32% compared to normotensive controls. In patients with the metabolic syndrome, AF risk may increase exponentially due to the combination of risk factors, including obesity, hypertension, diabetes mellitus and myocardial ischemia. Although AF can occur in structurally normal hearts, **left atrial dilatation** remains an important contributor for AF pathogenesis and embolic stroke risk.[44] The left atrium undergoes several morphological and electrical changes after the first AF episode.[45] These changes are mediated by IST (Figure 3).

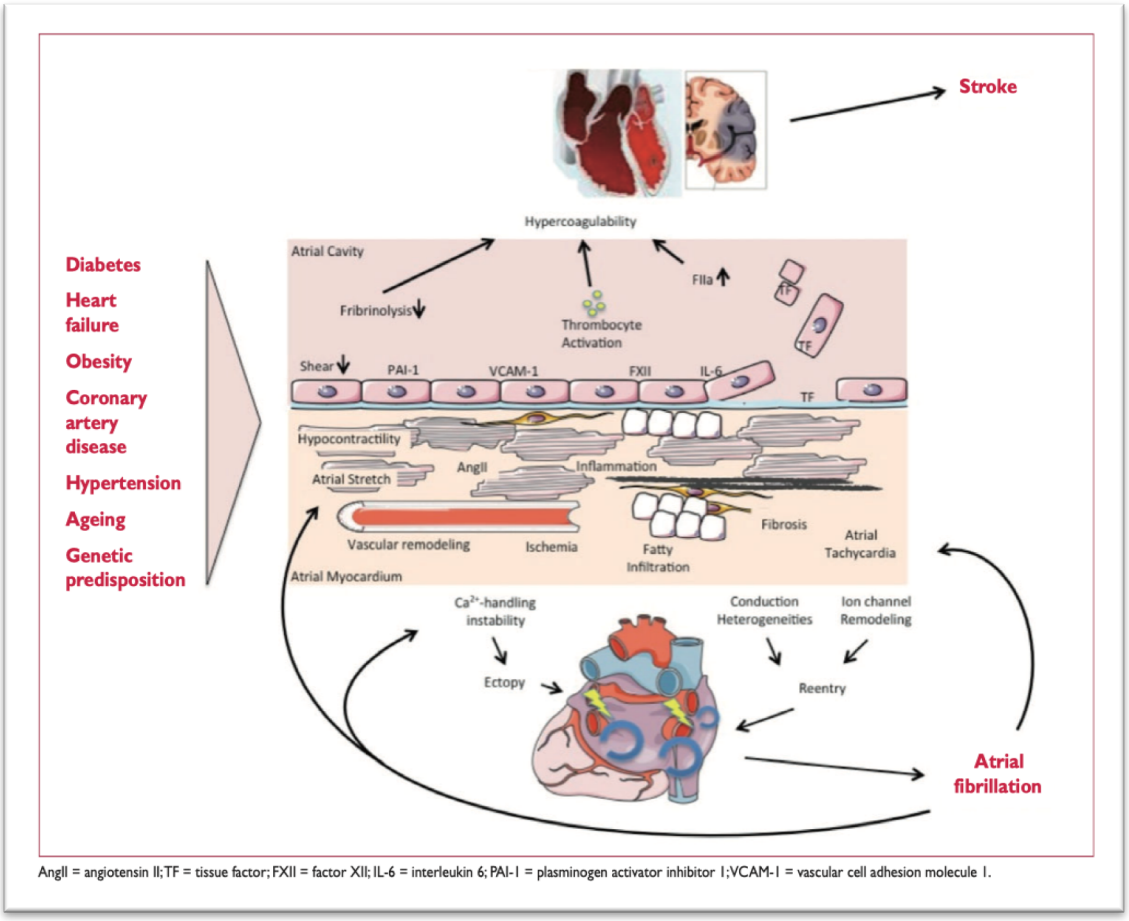


Figure 3. Pathogenesis of AF. Increased sympathetic tone links many of the components that promote AF and thrombo-embolism to vital organs. (Slide copied from ESC guidelines on Atrial Fibrillation: www.escardio.org/guidelines).[43]

Cytosolic calcium levels increase because of raised cAMP levels, driven by increased adrenergic stimulation of beta-1 receptors. This phenomenon, also referred to as "calcium signalling silencing", promotes electrical instability and electrical re-entry mechanisms.[46] IST also stimulates fibroblasts via aldosterone and purinergic signalling to produce interstitial collagen.[47, 48] Stretch-induced atrial fibrosis follows, which fractionates the depolarising electrical wave front. IST is also associated with increased inflammation, which may damage endocardial cells and expose the sub-endocardium.[49] Hypercoagulability, also mediated by IST, promotes left atrial appendage thrombosis and embolization to vital organs.[50]

AF subtypes and proposed management

The duration of AF is strongly associated with stroke risk.[51] **Paroxysmal AF**, which often self-terminates within seven days of onset, is a common complication of uncontrolled hypertension and HHD. This arrhythmia usually originates from the muscular sleeves inside the pulmonary veins where they enter the left atrium.[52] AF becomes "*persistent*" if it lasts more than seven days. "*Long-standing persistent*" AF has to be present for at least one year in a patient who agrees to rhythm control of his arrhythmia.

The **rhythm control** strategy of paroxysmal AF is controversial and can be accomplished by using either drugs or pulmonary venous isolation (PVI). Drug treatment with amiodarone, which is often life-long, is associated with dangerous side effects including thyroid dysfunction, corneal deposits, hepatic enzyme abnormalities and irreversible lung fibrosis. PVI, on the other hand, is performed under general anaesthesia with either "hot" or "cold" ablation in an attempt to electrically isolate the pulmonary veins from the left atrium. "Hot" ablation uses radio frequency (heat) energy to induce scar tissue around the pulmonary

venous ostia. “Cold” ablation uses liquid nitrogen to freeze the pulmonary venous-atrial junctions. The FIRE and ICE trial confirmed that cold ablation is as effective as hot ablation.[53] Radiofrequency ablation results in an improvement in the quality of life but even in the best hands, the rate of a second ablation over five years is about 50% and the recurrence rate in patients with persistent or chronic AF and underlying LV dysfunction is even higher. Despite these technological advances, the rates of major and minor complications are about 3% each although phrenic nerve palsy and most often fatal ALA-esophageal fistula are rare.[54] Even in patients undergoing pulmonary vein isolation/ablation if the CHADS-VASC score is 2 or more the current recommendation is that they remain on lifelong anticoagulation.[43]

The **rate control strategy** aims to reduce the ventricular rate by slowing atrio-ventricular (AV) conduction and can be accomplished with either AV blocking agents, e.g. beta-blockers or non-dihydropyridine calcium channel blockers. In difficult cases, AV-nodal ablation and permanent pacing can also be used as an alternative. This last-resort treatment is not ideal, because permanent single chamber pacing promotes dyssynchronous ventricular contraction, which may reduce cardiac output and trigger a pacing-induced cardiomyopathy. AV-nodal ablation with His-bundle pacing or biventricular pacing may be more suitable to preserve ventricular synchrony, but no randomised trial has been performed to date to test this hypothesis.[55] The patient with “**permanent AF**” agrees with his/her treating physician that a rate control strategy will be pursued. Lifelong oral anti-coagulation with warfarin or novel oral anticoagulants should be considered in all patients with a CHA_2DS_2-VASc score of ≥2, unless contraindicated. Patients with contraindications to oral anti-coagulants, e.g. an increased bleeding risk, may be candidates for left atrial appendage closure.[56]

Is upstream prevention of AF a possible "Holy Grail"?

Despite major advances in diagnosis and treatment, the current management of AF remains associated with increased morbidity and mortality. Upstream prevention of AF may therefore be a desirable treatment option for patients who have an increased risk of developing AF. It is interesting to note that lifestyle modifications have been shown to reduce incident AF.[57] Weight loss and increased physical activity can also restore cardiovascular autonomic function.[58, 59] The challenge with these recommendations is that they are very difficult to maintain, especially in the elderly. Modulating cardio-autonomic tone through device therapy remains an unexplored territory.

RATIONALE

Uncontrolled HT and HHD are the most frequent conditions that increase the risk to develop AF. The autonomic nervous system plays a central and mediating role in the pathogenesis and maintenance of non-valvular AF and as such, correcting **autonomic imbalance** may theoretically prevent AF in patients with HHD.

What is autonomic imbalance?

The autonomic nervous system consists of a sympathetic and parasympathetic system. During normal resting conditions, the parasympathetic system regulates the function of internal organs. The sympathetic system, which is also referred to as the "fight or flight system", becomes activated when the brain senses impending danger that threatens survival. Sympathetic activation normally does not last long, but failure to switch off this system can result in autonomic imbalance (AI). AI defines a state of relative IST and/or decreased parasympathetic tone. AI is associated with many diseases, including hypertension, heart

failure, atrial fibrillation, obesity and chronic kidney disease.[60-63] Our modern lifestyle of high stress levels, reduced exercise and diets rich in salt and carbohydrates undoubtedly fuels both the metabolic syndrome and AI.

AI and sudden cardiac death

Interestingly, AI is also associated with sudden cardiac death (SCD) during severe emotional stress.[64] Congenital long QT syndrome (LQTS) illustrates this association particularly well.[65] Symptomatic KCNQ1 mutation carriers with type 1 LQTS typically experience syncope, and sometimes SCD, during situations associated with IST, e.g. excitement, swimming or exercise. Conversely, higher resting vagal tone, seems to be protective and anti-sympathetic therapy, e.g. BB or left cardiac sympathetic denervation (LCSD), are now established therapies for type1 LQTS.[66] Another example where AI associated with and even predicted SCD came from a prospective cohort of apparently healthy young French male civil servants. Here, Jouven et al. used exercise-related heart rate profiles as surrogate markers of cardio-autonomic tone.[67] They found that faster resting heart rate (> 75 bpm), indicative of IST and slower post-exercise recovery of heart rate (< 25 bpm), indicative of reduced parasympathetic tone, is associated with and predicted a significantly higher SCD risk later in life. These findings were recently confirmed using heart rate recovery at 10 seconds after cessation of exercise as a predictor of cardiovascular death in a prospective cohort of > 40 000 UK Biobank participants.[68] Heart rate profiles during exercise and recovery can therefore be used as surrogate markers of cardio-autonomic tone and may also be inherited.[69, 70] The heritability of these responses, which is really a reflection of the propensity of the heart and brain to behave in a certain way during fight- or flight (hyper-adrenergic) situations, may partly explain the familial clustering of SCD.[71]

The heart, however, is not the only organ that feels the brunt of acute sympathetic activation: the kidneys are probably affected more chronically. They play an important regulating role which, in essence, augments overall sympathetic tone. The afferent renal nerves, mostly located in the renal pelvis, transmit signals via the dorsal spinal cord to the brain when activated by stretch forces (Figure 4).[72] Activated centres in the brain include the nucleus tractus solitarius, the medulla oblongata and the paraventricular hypothalamic nuclei.

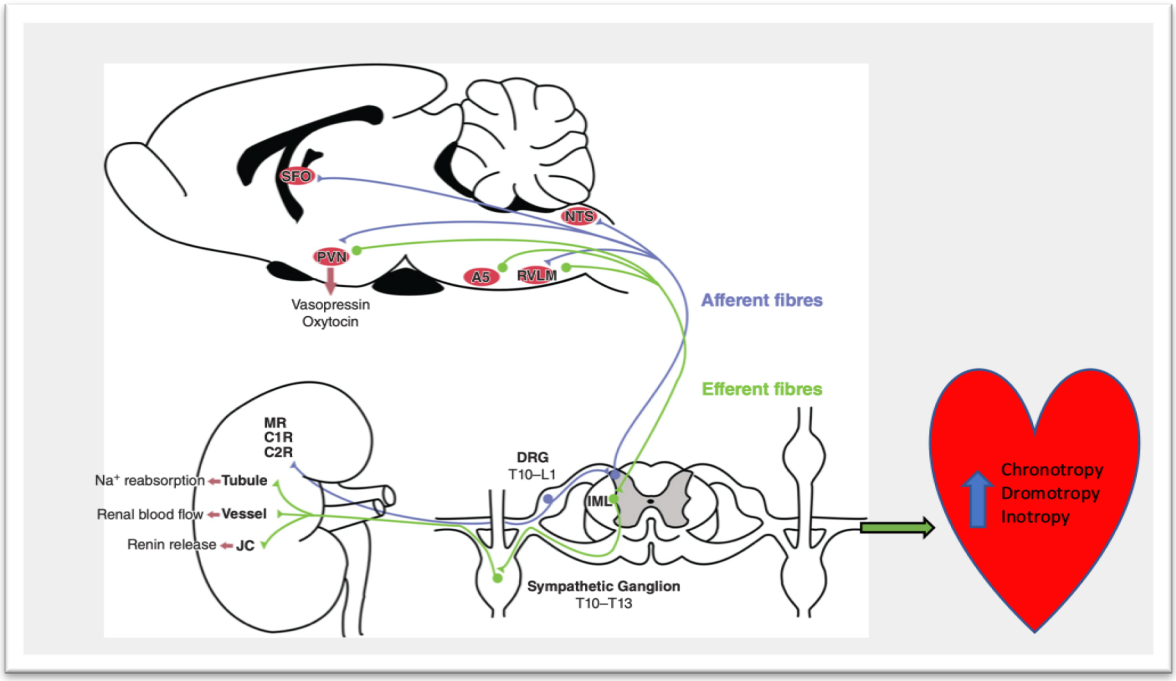


Figure 4. Renal nerves facilitate brain-kidney sympathetic cross talk and play a central role in the regulation of blood pressure and autonomic tone. SFO: subfornical organ; PVN: paraventricular nucleus of hypothalamus; RVLM: rostral ventrolateral medulla; NTS: nucleus tractus solitarius; IML: intermediolateral cell column. (Adapted from: Nishi EE, et al.[72])**.**

These renal **afferent** nerve signals increase vasopressin and oxytocin release accompanied by **increased activation of efferent sympathetic neurons**. These efferent neurons run along paravertebral ganglia and large blood vessels, where they exit to vital organs located in the thoraco-lumbar region. In the thorax, sympathetic nerves terminate in the sino-atrial node,

atrio-ventricular node and ventricles. Here, sympathetic stimulation increases chronotropy, dromotropy and inotropy, respectively. Cumulatively, these effects increase cardiac output and systolic blood pressure. The sympathetic nerves also pass through the stellate ganglia, which plays an important regulatory role in the propensity to develop tachyarrhythmias, e.g. ventricular tachycardia or atrial fibrillation.[73]

In the lumbar region, the **efferent** sympathetic nerves enter the kidneys via the renal arteries. They arborise alongside the renal artery, run in the vasa vasorum and terminate in the efferent glomerular arteriole, the juxta-glomerular apparatus (JGA) and the renal tubules. JGA activation results in renin release, which activates the renin-angiotensin-aldosterone system (RAAS). The end products of RAAS activation, angiotensin II (AT-II) and aldosterone, induce vasoconstriction and renal tubular sodium and water retention, respectively. AT-II constricts the efferent glomerular arteriole, which raises intra-glomerular pressure and filtration rate. AT-II also increases peripheral resistance, which increases diastolic blood pressure, cardiac afterload and coronary perfusion, respectively.

In the normal kidney, stretching of the renal pelvis inhibits the efferent sympathetic renal nerves. In the hypo-perfused kidney, however, the inhibitory reflex is attenuated and results in sympatho-exitation, increased cardiac output, augmented glomerular filtration and subsequent adrenal gland activation. Chronic and inappropriate activation of this system results in hypertension and its sequelae. Although IST is not the only cause of essential hypertension, there is strong evidence that the sympathetic nervous system plays a critical role in hypertension pathogenesis and endothelial health.[74]

Modifying this system by cutting the nervous communication between the brain and the kidneys [renal denervation (RD)] may therefore not only improve renal perfusion, but also benefit the whole vascular tree and organ blood supply through pleiotropic effects.

The kidneys play a central role in autonomic dysfunction

The kidneys play a pivotal role in the pathogenesis of hypertension through autonomic regulation of increased peripheral resistance, sodium and water retention and other mechanisms.[72] Anatomical and physiological knowledge of the renal nerve supply supports the hypothesis that RD lowers blood pressure and consequently produces beneficial cardiac effects.[73-76]

Renal denervation and its effect on hypertension

The hypothesis that denervation of the renal sympathetic nerves results in blood pressure reduction was successfully tested in unblinded clinical trials without a sham-control procedure. In humans, non-selective surgical splanchnicectomy, which includes RD, was frequently performed as primary hypertension treatment[77], but unacceptable iatrogenic side-effects, e.g. impotence, orthostatic hypotension and incontinence, led to its disappearance from current-day practice. The advent of endovascular therapy made access to the renal arteries and nerves possible through femoral artery puncture. Radiofrequency heat energy is applied through a dedicated helical catheter to sear and destroy the adventitial renal nerves (Figure 5).

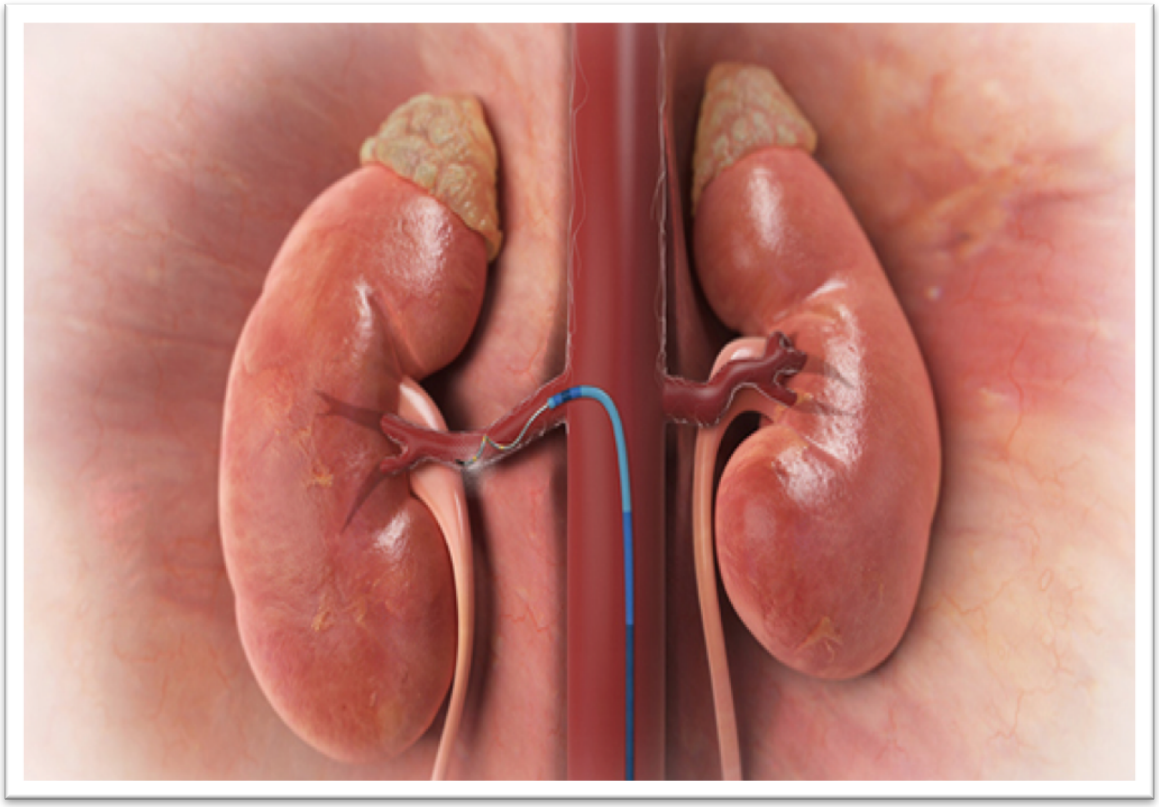


Figure 5. Renal denervation performed with a Symplicity Spyral catheter via femoral arterial access. (Permission obtained from Medtronic to publish the picture).

Heradien et al. recently reported that RD could also be performed via brachial or radial artery puncture (Addendum).[78] This form of RD vascular access eliminates the risk of groin-related hypertensive arterial bleeding and allows same-day hospital discharge. Although RD aims to essentially reduce brain-kidney sympathetic crosstalk, most of the experimental and clinical data we have to date focus on the ability of RD to reduce blood pressure.

Landmark RD trials

The series of landmark endovascular RD trials are often colloquially referred to as the 'Symplicity HTN Trilogy'. The first trial that kindled interest was published a decade ago. **SYMPLICITY HTN-1** was a multicentre, non-randomised, safety and proof-of-principle cohort

study.[79] Patients with so-called "resistant HT", defined as an office BP ≥ 160/90 mmHg on three antihypertensive drugs including a diuretic, underwent percutaneous bilateral RD. Compared to baseline, office blood pressure at six months follow-up (6MFU) was reduced by 22/11 mmHg. Importantly, renal noradrenaline spillover was reduced by 47% (95% CI: 28–65%), signifying that RD treatment is associated with a reduction in sympathetic tone.

SYMPLICITY HTN-2 was the first randomised controlled trial (RCT) that tested the hypothesis that RD was superior to medical therapy in the management of resistant HT.[80] Again, even more impressive than in HTN-1, office systolic BP was reduced with RD by 32 mmHg at 6MFU. This trial resulted in an all-time high interest that RD might add an important new weapon in the fight against hypertension. Whereas the procedure was registered for use in European countries, the FDA insisted on a further trial before registration in the USA; hence, the SYMPLICITY HTN-3 trial was designed.[81]

SYMPLICITY HTN-3 randomised 535 treatment-resistant hypertensive patients to RD or sham-RD. The results were interesting, but unexpectedly disappointing. Although both groups had significant office blood pressure reductions at six-month follow-up, RD did not meet the primary efficacy endpoint of superior office blood pressure reduction, compared to a sham-RD procedure. These surprising results brought the "speeding RD train to a grinding halt".[82] However, several confounders have been identified that may have contributed to the failure of SYMPLICITY HTN-3.

Possible confounders in HTN-3

Despite a rigorous trial design and execution, several unaccounted factors may have contributed to HTN-3's failure to demonstrate RD efficacy relative to sham control.[83] These include patient demographics, medication adherence, "Hawthorne effect", placebo effect, trial conduct, regression to the mean, operator experience and catheter design.

Patient demographics

Unlike previous SYMPLICITY trials, HTN-3 also recruited African American (AA) patients (26% of the prospectively stratified cohort). Compared to the non-AA sub-group, AA patients in the sham group had a 9.2 mmHg greater decline in office systolic blood pressure (SBP) at 6MFU. This change in sham office SBP was nearly twice as large in AA compared to non-AA patients. In a post-hoc analysis, the authors concluded that this unexpected BP reduction in the sham group is likely due to increased post-randomisation medication adherence and that the change after renal denervation was probably not confounded by race.[84] Although this exploratory report does not provide definitive evidence that the SBP response to RD differed by race, it is generally accepted that hypertensive patients of African ancestry are poor responders to angiotensin-converting enzyme (ACE)-inhibitor and BB therapy.[85] This view was recently challenged in the Creole study where investigators found that Black Africans respond better to perindopril-amlodipine than to perindopril-thiazide combination therapy.[86] Despite these encouraging results that Black Africans may respond to ACE-inhibitor therapy, it remains to be proven that Blacks are poor RD responders.

The beneficial effects of RD may be attenuated in patients with late-stage peripheral artery disease, or increased vascular stiffness, which might limit the capacity for reverse vascular

remodeling following the procedure. Indeed, several reports indicate that various indices of increased arterial stiffness predict improved blood pressure response following RD.[87-89] Likewise, Ewen et al. showed in a retrospective analysis that patients with isolated systolic hypertension, a coarse but easily-determined identifier of increased arterial stiffness (defined as office SBP > 140 mmHg and DBP < 90 mmHg), had less pronounced blood pressure drops than patients with combined systolic and diastolic hypertension.[90] For this reason, patients with isolated systolic hypertension were explicitly excluded from the sham-controlled randomised controlled trials (RCTs) that followed SYMPLICITY HTN-3.

Medication adherence

Although patients were encouraged to continue taking their prescribed medication diligently throughout follow-up, urine or blood levels of anti-hypertensive drugs were not measured in SYMPLICITY HTN-3. Surprisingly, about 40% of the patients changed their antihypertensive medication regime after randomization. Non-adherence may be due to multiple factors including lack of understanding the risks and benefits of hypertension therapy, socioeconomic factors limiting drug access, social support, depression and anxiety and regimen complexity and side effects. Taken in context with the significant drop in blood pressure in the sham group, it is reasonable to suspect that unpredictable variable adherence to antihypertensive medication may have impacted the results of SYMPLICITY HTN-3. This concern led to the design of “off-medication” trial designs following SYMPLICITY HTN-3.

Hawthorne and placebo effect

The Hawthorne effect describes the adjusted behaviour of trial participants to seemingly please/impress study investigators.[91] Examples of such behaviour include increased

medication adherence and patients reducing their salt intake and exercising more regularly. It is difficult, if not impossible, to prevent this type of behaviour. The placebo effect may also have played a large role in SYMPLICITY HTN-3, resulting in a significant reduction in office SBP in the sham group.

Regression to the mean (RTM)

RTM is defined as the tendency for an extreme measurement on one occasion to become less extreme when measured again. This may explain why, unlike previous SYMPLICITY trials, HTN-3 showed only a 4.1 mmHg between-group SBP treatment difference. To reduce this problematic statistical phenomenon, statisticians recommended that, rather than a Student t-test, analysis of covariance (ANCOVA) might be a more appropriate test to use in future RD trials.[92] Finally, it is essential to note that the potential biases introduced by both the Hawthorne effect and regression to the mean can be addressed by randomisation.

Operator experience and Catheter design

In Symplicity HTN-3, 112 operators performed an average of 3.3 procedures per operator.[78] Less than five procedures were performed per site, and > 50% of the operators performed ≤ 2 procedures in the trial. Several technical challenges may face an inexperienced operator: difficult intubation with poor guide catheter back-up, accessory polar renal arteries (smaller than main vessel) that could not be treated, the "hostile" groin, e.g. morbid obesity and inability to visualize anatomically whether a successful 4-quadrant ablation was performed, using a 2D fluoroscopic image. Operators were also instructed to avoid distal renal arteries. However, Sakakura et al. subsequently discovered that in human cadavers, the renal nerves run closer to the arterial lumen distal to the renal bifurcation, than proximally (2.6 mm

vs 3.4 mm).[93] These sites, although being typical “sweet spot targets” for denervation, were thus missed in most cases. Animal studies have shown that RDN success is very much dependent on distal denervation.[94,95]

The Flex catheter (Medtronic Inc.) is a single point denervation system that uses a proprietary algorithm of retraction, flexion and rotation to focus radiofrequency energy points in recommended anatomical sites of the renal artery. The Medtronic flex catheter was similar although apparently not identical to that used in the SYMPLICITY 1 and 2 trials which demonstrated approximately a 30mmHg drop in office systolic blood pressure. It was technically challenging to perform enough 4-quadrant ablations with the old catheter, but the next generation Symplicity Spyral catheter (Medtronic, Inc), which is an over-the-wire system, is a safer, more intuitive system than not only associates with more 4-quadrant ablations but also enables the operator to safely perform distal ablations, without the danger of perforation or dissection (Figure 6).

The Spyral system typically requires less fluoroscopy time with less ionizing radiation and lower doses of iodine contrast agent resulting in better renal function outcomes post-procedurally. Although the Spyral system measures vascular impedance as a surrogate marker of adventitial neural damage, a reduction in vascular impedance does not necessarily mean the perivascular nerves have been destroyed.

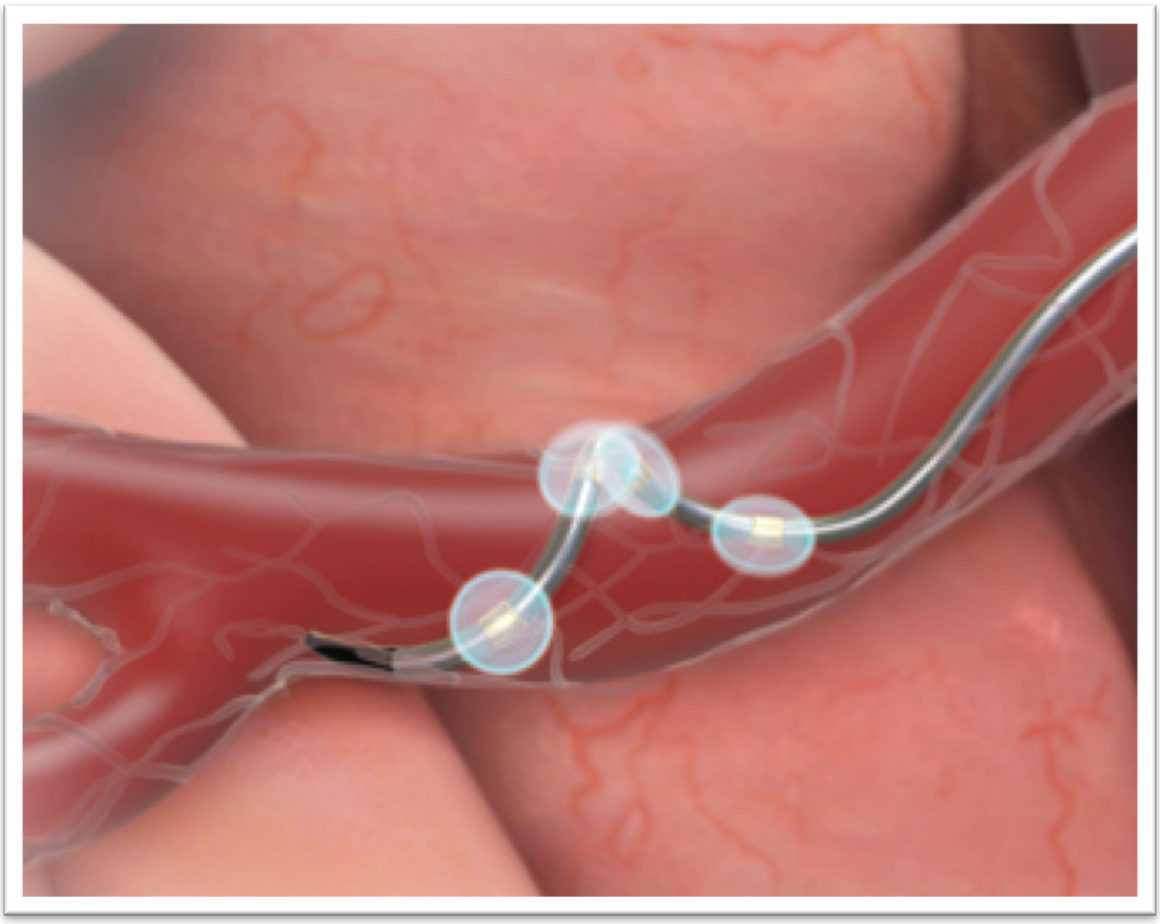


Figure 6. Radio-frequency heat energy is applied for one minute with a Symplicity Spyral catheter* to sear the adventitial renal sympathetic nerves. (*Medtronic® - Permission obtained from the company to publish the picture)

A new generation of sham-controlled renal denervation RCTs

Recently reported positive results from three new randomized sham-controlled trials might have rekindled interest in RD. All three trials were designed to compensate for the confounding factors identified in HTN-3. Although smaller in scope than HTN-3, the sham-controlled **SPYRAL HTN-OFF MED** trial tested the hypothesis that RD would reduce BP in the absence of anti-hypertensive drugs.[96] Patients with milder HT were asked to discontinue their BP medication for at least one month before and during the trial duration. Similar to HTN-3, patients were randomised to RD or sham-RD. Compliance was checked with urine drug levels throughout the trial. RD was performed by experienced proceduralists, who also denervated

the distal renal arteries with a second-generation quadripolar catheter (Symplicity Spyral). Results were reported at three months and, albeit to a lesser degree than previous trials, showed that RD reduced office and ambulatory BP in hypertensive-drug naïve patients more than a sham-RD procedure, thus confirming the proof-of-concept.

The sham-controlled **SPYRAL HTN-ON MED** trial showed similar, if not greater, improvements in both office and 24-hr blood pressure six months post-RD in a similar population treated with one to three antihypertensive agents.[97]

Finally, the sham-controlled **RADIANCE-HTN SOLO** trial employed a design quite similar to SPYRAL HTN-OFF MED but used an ultrasound-based catheter denervation system (Otsuka/ReCor Paradise).[98] The trial recruited 146 patients and patients were to remain off antihypertensive medications throughout the two months of follow-up. Interestingly, this catheter is only advanced into the main vessel, not into the distal renal arteries. The results after two months showed a significant reduction in daytime systolic ambulatory blood pressure and no major adverse events were reported in either group.

Together, these trials energised endovascular RD and provided the much-needed hope that RD does lower blood pressure in selected patients when the right technique is used by experienced renal denervationists. Typically, the best responders to RD would be patients with chronically increased IST e.g. resting heart rate > 75 beats/min in BB-naïve patients or patients who exhibit non-dipping nocturnal blood pressure during ambulatory monitoring.

One of the major limitations of our current knowledge base is that we are unable to identify RD responders from non-responders with any degree of accuracy.

Is there a knowledge gap: does RD have anti-fibrillatory potential?

In the past, most RD trials have focused on blood pressure-lowering, hoping that RD will provide the cure for the "silent killer". Very little data, however, have been reported about the **anti-arrhythmic potential of RD**, and specifically the feasibility of RD used as "upstream therapy" to prevent non-valvular AF.

Anti-fibrillatory effects of RD: animal data

Canine studies with long-term intermittent atrial pacing suggest that RD induces morpho-electrophysiological changes that modify the AF substrate.[99] These animals underwent right ventricular pacing for three weeks at 240 bpm, which induced heart failure (HF) similar to so-called "tachy-cardiomyopathy." In dogs with HF randomised to RD, compared to dogs with HF without RD, it was more difficult to induce AF during ganglionated plexi stimulation. One year later, the same group showed in a model of intermittent atrial pacing (8 hours/day for 12 weeks) that left atrial structure and function were significantly improved in the RD group, compared to the sham group and that atrial fibrosis was also significantly reduced in the RD group.[100] RD dogs had significantly fewer AF incidents and shorter AF duration. Compared to sham-control dogs, electrophysiological changes in RD canines included an increased atrial effective refractory period and AF cycle length and a decreased P-wave duration and P-wave dispersion.

Anti-fibrillatory effects of RD in humans

Meta-analyses of human studies have shown that RD is associated with regression of both left ventricular hypertrophy (LVH) and left atrial dilatation.[101] Meta-regression analysis, however, failed to demonstrate a significant relationship between RD-induced LV mass index reduction and BP at lowering at six months. This finding suggests that regression of LVH seen with RD may occur independently of BP changes. Recently, a small RCT showed that RD may reduce AF triggers and AF burden in patients with hypertension and paroxysmal or persistent AF.[102] Pokushalov, et al. was the first to demonstrate that, **when RD is added to PVI**, incident AF is reduced.[103] The trial recruited 27 patients: 9 of 13 (69%) who had RD were AF-free one year after PVI, compared to 4 out of 14 (29%) who did not have RD (p = 0.033). Several points of criticism were raised in a letter to the Journal editor: the main concern was the small sample size.[104] Other concerns included changes in design and inclusion and exclusion criteria e.g. AF recurrence at one year was not a prespecified endpoint and a lack of detailed methods description e.g. the type of catheter used to stimulate the renal nerves. Five years later, the same group showed similar results after unconventionally combining data from two RCT's: this time AF burden was confirmed with an implantable cardiac monitor.[105] To date, no RCT has tested the feasibility of upstream RD treatment as a stand-alone therapy (without PVI) to prevent AF in patients with HHD.

PROBLEM STATEMENT

RD treatment may prevent non-valvular AF in patients with HHD.

RESEARCH QUESTION

Can RD prevent non-valvular AF and restore autonomic imbalance in patients with HHD?

HYPOTHESIS

The current study tested the hypothesis that RD prevents non-valvular AF in patients with HHD.

AIM

To investigate the efficacy of RD as an anti-arrhythmic tool to preventing non-valvular AF in patients with HHD.

OBJECTIVES

1. Demonstrate that RD treatment reduces incident, non-valvular AF in patients with hypertensive heart disease (primary efficacy endpoint).
2. Demonstrate that RD treatment is associated with secondary endpoints, including:
    a. reducing office blood pressure six months follow-up (6MFU)
    b. reduced cardiovascular events including cardiovascular death and myocardial infarctions
3. Demonstrate that RD treatment is associated with restoration of autonomic imbalance by:
    a. reducing resting heart rate at 6MFU
    b. improving vagal tone by improving heart rate recovery post exercise at 6MFU

CHAPTER 2

STUDY DESIGN

Pre-specified outcomes

It was hypothesised that RD can prevent AF (**primary efficacy end point**) in patients with HHD. For this prespecified, primary endpoint a prospective, single-blind, randomised, sham-controlled trail was designed. Although the study was not powered to detect a statistically-significant difference in **secondary end points,** restoration of autonomic imbalance, 6MFU office and ambulatory blood pressure and cardiovascular endpoints (cardiovascular death, myocardial infarction [non-ST elevation and ST-elevation myocardial infarction with troponin leaks] and stroke [permanent neurological deficit] or transient ischemic attack [transient focal neurological deficit of < 24 hours duration]) were also assessed. It was also of interest to report the effect of RD on echocardiographic parameters, ECG-derived markers of autonomic tone and cardiac arrhythmia burden at 6MFU.

Sponsor/ethical approval/study number/informed consent

Medtronic (Inc.) sponsored the trial and provided renal denervation catheters, implantable loop recorders and patients transport fee reimbursement. The sponsor did not have access to the data. The study was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University and allocated the study number M12/10/049. The study complied with the guidelines and stipulations of the Helsinki Declaration. Annual reports had to be submitted to the HREC regarding adverse outcomes, including death, withdrawal from the study or study-associated complications. Eligible patients provided written informed consent and could withdraw from the study at any time. Treating physicians were informed that their patient was participating in a clinical trial. Patients participating in the study were encouraged

to take their medication regularly, but pill counts or urine drug levels were not performed to ascertain drug adherence.

Clinical history and physical examination

Every patient underwent a clinical history taking (anamnesis) and physical examination before randomisation. Patients were questioned about dyspnea grade and precipitants, angina, palpitations or leg swelling. Diabetes mellitus status, statin, aspirin or warfarin usage, previous coronary artery disease (CAD) (previous myocardial infarction, stents or coronary artery bypass surgery), previous stroke (embolic or hemorrhagic) or transient ischemic attack (reversible neurological deficit that disappeared in 24 hours), peripheral arterial disease symptoms (claudication, rest pain, etc.) were ascertained. Although most people with sleep disorders are often undiagnosed, patients using continuous positive airway pressure (CPAP) devices were regarded as having obstructive sleep apnea. Patients were asked about previous cardiac arrhythmic events (e.g. atrial flutter or fibrillation; ventricular tachycardia), electrical or chemical cardioversion and the use of anti-arrhythmic drugs. Patients were also asked about allergies against penicillin and iodine (used during angiography).

Peripheral pulses were palpated and the carotid pulses auscultated for bruits and palpated for volume and pulse wave characteristics. If pulses were of equal volume in both arms, blood pressure was taken on the left upper arm with an automated device (Omron M3) and a large cuff after five minutes of rest. The apex beat was palpated and a heaving apex beat was indicative of clinical left ventricular hypertrophy. The heart was auscultated for the presence and loudness of S1 and S2, additional cardiac sounds and audible murmurs, respectively. The lungs were auscultated for bibasal crackles. The abdomen was palpitated for the presence of

a pulsation that may indicate an abdominal aortic aneurysm, auscultated for bruits indicative of renal artery stenosis and fundoscopy performed to look for signs of hypertensive or diabetic retinopathy. Urine dipstick tests were performed to exclude proteinuria, glycosuria or hematuria. Urine was sent to the laboratory for microscopy, culture and sensitivity, if positive on dipsticks for leucocytes or nitrites.

Due to funding limitations, this investigator-driven, single site pilot study did not have a data and safety monitoring board (DSMB). Furthermore, a DSMB was not an ethical pre-requisite.

Special investigations

Every screened patient underwent a standard transthoracic echocardiogram performed by experienced cardiac technicians who were blinded to the patients randomisation status. Echo-images were captured with a VIVID (General Electric) echo machine in the parasternal long and short axis and apical two-and four-chamber views. Images were saved electronically for further analysis. Patients underwent a standard Bruce-protocol treadmill exercise stress test (EST). Blood pressure was taken every minute during and after the test using an automated blood pressure cuff. The EST was terminated if the patient reached at least 80% of their target heart rate or developed tiredness with the inability to exercise further. Patients experiencing chest pain, hypotension, significant cardiac arrhythmias or ST segment shifts during/immediately after the test were considered to have a poor prognostic stress ECG test requiring invasive coronary angiography. Qualifying patients were also fitted with a 24 hr ambulatory ECG recorder and automated blood pressure monitoring (ABPM) device (Mortara) for home heart rhythm and blood pressure monitoring, respectively. Data obtained from these devices were analysed by experienced cardiac technicians unaware of the

patient's randomisation status. Baseline blood tests included sodium and potassium serum level and an estimated glomerular filtration rate (eGFR). Patients fulfilling all the inclusion criteria were invited to participate in the study and asked to sign an informed consent. Those with any exclusion criteria were thanked for their screening visit, but not included in the study.

Inclusion Criteria:

1. Age ≥ 55 years
2. Office blood pressure ≥ 160/90 mmHg in non-diabetics or ≥ 150/90 mmHg in diabetics
3. Subjects must be on at least three anti-hypertensive drugs, including a diuretic agent
4. Sinus rhythm
5. Left ventricular hypertrophy defined on echo defined as:
    a. Estimated LV mass > 255 g or LVMI > 115 g/m^2 for men
    b. Estimated LV mass > 193 g or LVMI >95 g/m^2 for women

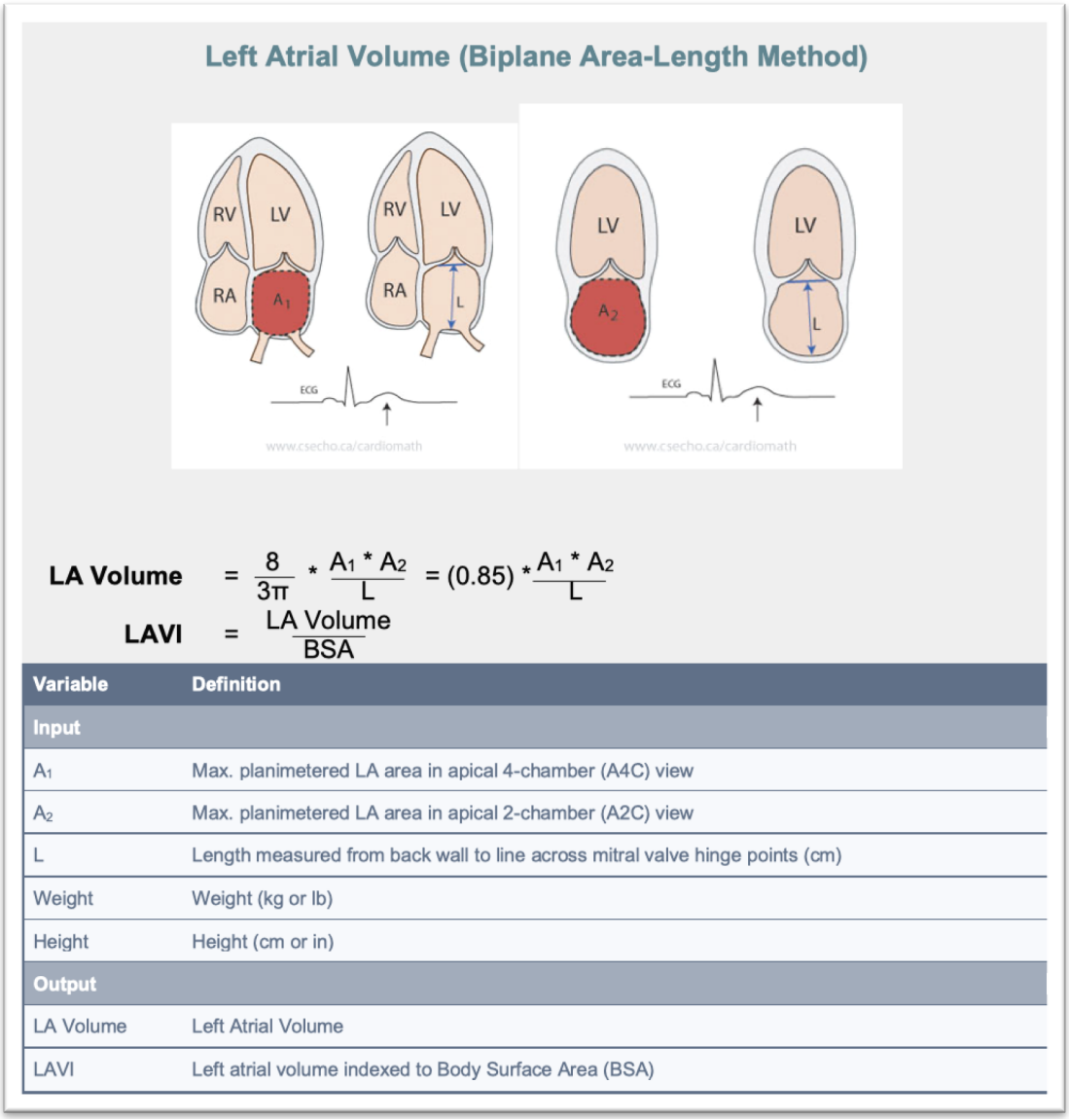
    LV mass was calculated with the Devereux formula, where:

$$\text{LV Mass (g)} = 0.8\{1.04[([\text{LVEDD} + \text{IVSd} + \text{PWd}]^3 - \text{LVEDD}^3)]\} + 0.6$$

Abbreviation		Meaning of abbreviation
LVEDD	:	Left Ventricular End-diastolic dimension (mm)
IVSd	:	Interventricular septal wall dimension during diastole (mm)
PWd	:	Posterior ventricular wall dimension during diastole (mm)

6. Must have an indication for coronary angiography with a positive stress ECG with/without angina or angina equivalent e.g. dyspnea. A positive stress ECG was defined as ≥ 1 mm ST segment shift (depression or elevation) in ≥ 2 contiguous leads.

7. Evidence of left atrial dilatation, defined as a left atrial diameter of ≥ 45mm on either M-Mode or two-dimensional (2D) measurement **or** a Left Atrial Volume Index (LAVI) ≥ 34 ml/m^2, which was calculated by determining the left atrial area in the apical four- chamber and two-chamber views, respectively. This product was then multiplied by 0,85 and divided by the shortest perpendicular distance from the coaptation point of the mitral valve leaflets (Figure 7). A blinded, experienced clinical technician must perform the echocardiogram.



Variable	Definition
Input	
A_1	Max. planimetered LA area in apical 4-chamber (A4C) view
A_2	Max. planimetered LA area in apical 2-chamber (A2C) view
L	Length measured from back wall to line across mitral valve hinge points (cm)
Weight	Weight (kg or lb)
Height	Height (cm or in)
Output	
LA Volume	Left Atrial Volume
LAVI	Left atrial volume indexed to Body Surface Area (BSA)

Figure 7 Biplane method for calculating Left Atrial Volume Index (LAVI): Source:http://www.csecho.ca/wpcontent/themes/twentyelevencsecho/cardiomath/index.php?eqnHD=echo&eqnDisp=lavolbpm

Exclusion Criteria:

1. Estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73m^2
2. Renal artery anatomy unsuitable for RD
3. Significant valvular heart disease e.g. moderate/severe valve stenosis or regurgitation
5. Untreated thyroid disease, e.g. thyrotoxicosis
6. Patients needing to undergo coronary artery bypass surgery

Randomisation

Consenting patients were randomised using a computer-generated number sequencer (https://numbergenerator.org/) and a closed envelope system. Although the patient was blinded, only the researcher was aware of whether the patient had been allocated to the active or sham RD arm. Allocation status was only revealed to the patient at the end of the study or during life-threatening emergencies, e.g. severe hypotension or hypertensive emergencies.

Definition of autonomic imbalance

Autonomic imbalance (AI) was defined as the presence of one or more risk factors being present:

1. resting heart rate (RHR) >75bpm, signifying IST
2. peak exercise heart rate minus one minute exercise recovery heart rate (HRR) <25bpm, signifying reduced vagal/parasympathetic recovery tone.

Statistical considerations: sample size calculation and between-group comparisons

The Stellenbosch University Department of Biostatistics assisted with statistical calculations which were performed with SPSS software (IBM Corporation). No study was previously published on upstream preventative treatment of AF. The main screening purpose was to recruit a study population with a **relatively high risk to develop AF** that can be detected by an implantable cardiac monitor over a relatively short period of time. In this regard, older people with hypertension, coronary artery disease and HHD (left ventricular hypertrophy and left atrial dilation) were considered ideal candidates for the study. The ASSERT study investigated the incidence of device (pacemaker or implantable cardioverter defibrillator)-detected subclinical AF (SAF) and the risk of stroke in older, hypertension-treated patients.[106] The 3-month SAF incidence was 10.1%. SAF incidence in the present study was predicted in 40% in the sham group after a three-year follow-up and of 10% in the RD treatment group, respectively. Power was set at 80%, alpha at 0.05 (probability of a type I error) and beta at 0.2 (probability of a type II error). This resulted in a sample of 31 patients in each arm (n = 62). The sample size was increased to 90 patients to account for loss to follow-up and attrition, study-withdrawal and death. Subsequent to the current study protocol which was conceptualised in 2013, Reiffel et al, reported in the REVEAL AF study an event rate of 40% at 30 months in patients without avert atrial fibrillation who had an implantable loop recorder placed.[107] This information was not available at study conception, but seems to support the sample size calculation. The log-rank test was used to calculate the cumulative incidence of the primary endpoint with a Kaplan-Meier graph. Analysis of covariance (ANCOVA) and student's t-test (paired and unpaired) were used to compare means intra-group (baseline vs 6-month follow-up) and between groups, respectively. Fisher's exact test was used to compare proportions/frequencies. A P-value of < 0.05 was considered significant.

INTERVENTIONAL PROCEDURES

Diagnostic coronary angiogram

Non-fasting patients were admitted to a general medical ward and instructed to take his/her regular medication. To reduce the risk of iodine contrast-nephropathy, the patient was pre-treated with one liter of normal saline over four hours. The patient was given a mild oral sedative (Lorazepam: 1 mg sublingually) in the ward before transfer to the cardiac catheterisation laboratory. ECG monitor stickers and an automated blood pressure cuff were placed on the patient's contralateral arm (arm not used during coronary catheterisation). The patient's right groin area and right forearm were shaved and cleaned with Hibitane® cleaning solution. The patient's left forearm was only prepared if he/she previously had coronary artery bypass surgery to enable intubation of the left internal mammary arterial graft. The patient was covered with a sterile drape.

The skin over the radial artery was injected with 5% Lignocaine and the radial or femoral artery punctured with a sterile, hollow steel needle. The modified Seldinger technique was then used to canalise the artery. After inserting a sheath into the radial artery, if used for arterial access, it was flushed with a mixture of nitrates, Verapamil and heparinised saline. Coronary angiography was performed using either a 5 French diagnostic Tigue catheter (radial artery) or 6 French diagnostic left and right Judkins catheter (if the femoral artery was punctured). Significantly narrowed epicardial arteries with a lumen diameter narrowed ≥ 70% were treated according to the performing cardiologist's judgement. Complex CAD for possible bypass surgery was discussed with and referred to the cardiothoracic surgeon, if clinically indicated.

Renal denervation

Both renal arteries were injected with iodine-containing ionizing contrast dye to delineate its anatomy and ascertain the presence of accessory renal arteries. [108] After pre-treatment with 5 ml of nitrates intra-arterially and 5000 IU heparin intravenously, a balanced middleweight guidewire (BMW; Abbot) was threaded through a short 6-French Amplatz guiding catheter down the renal artery under X-ray fluoroscopic guidance into the distal renal artery branches. In patients randomised to active treatment, the quadripolar, Symplicity Spyral renal denervation catheter (Medtronic Inc.) was threaded over the guidewire into a distal renal artery. The guidewire was pulled back into the guiding catheter, and the denervation conformed to the vessel wall in a spiral fashion, hugging the vascular endothelium (Figure 6, above). Radiofrequency heat energy up to 70 °C was applied for one minute after giving the patient 2 ml of intravenous morphine sulphate (10 mg/10 ml) for analgesia. The guidewire, which was withdrawn into the main renal artery, was threaded back over the denervation catheter. The guidewire was then steered into another distal artery attempting to denervate each distal polar artery with at least four denervation sites. Finally, the main vessel was treated with at least eight denervation sites. The same procedure was repeated on the contra-lateral or accessory renal arteries.

Sham renal denervation

In patients randomised to the sham-arm, contrast dye was injected into the renal artery, but the guidewire was not passed down the artery. Pre-recorded renal denervation machine sounds were played during the sham procedure and saline was injected as a mock painkiller, if they complained of pain during the angiogram.

After both renal arteries were treated, the guide catheter and guidewire, if used, were removed and the puncture site was either sealed with an Angioseal® closure device for femoral artery punctures or compressed with an inflatable armband (Terumo®) for radial artery punctures.

Insertion of implantable loop recorder (ILR)

Every patient, regardless of randomisation allocation, had a subcutaneous ILR (Reveal XT: Medtronic) implanted upon completion of the vascular intervention. The skin over the sternal area was sterilized with Hibitane solution, and the parasternal left fourth intercostal space was infiltrated with 5% Lignocaine. A 2 cm-incision was made over this space and anchoring sutures were placed at opposite angles of the wound. The ILR was inserted subcutaneously and tied to the anchoring sutures to prevent dislodgement. The subcutaneous layer and skin were sutured separately with chromium and nylon (V-lock®), respectively. Every patient was given 2 g of intravenous Cefazolin to reduce the risk of skin infection. The wound was covered with a waterproof, sterile plaster (Opsite®), and the patient instructed not to remove the plaster until two weeks have passed. The patient was taken back to the general medical ward, the saline infusion was completed, and the patient was discharged the same day if he/she had a radial procedure. Patients who had a femoral arterial puncture were observed overnight in the general medical ward.

Follow-up

Patients who were referred for coronary artery bypass surgery remained included in the trial. Patients were followed up at six-monthly intervals for the primary efficacy end point, by scanning the ILR and performing a 12-lead ECG with each visit. Prespecified secondary endpoints were also recorded.

CHAPTER 3

RESULTS

Recruitment and randomisation

Between 1 March 2013 and 31 August 2018, a total of 800 patients were screened for eligibility, out of which 717 patients did not meet the entry criteria or declined to participate (Figure 8). Eighty-three patients were randomised, one patient in the RD group withdrew informed consent and one patient in the sham group could not be traced: complete data sets were available for 80 patients (RD: 42 and sham RD: 38).

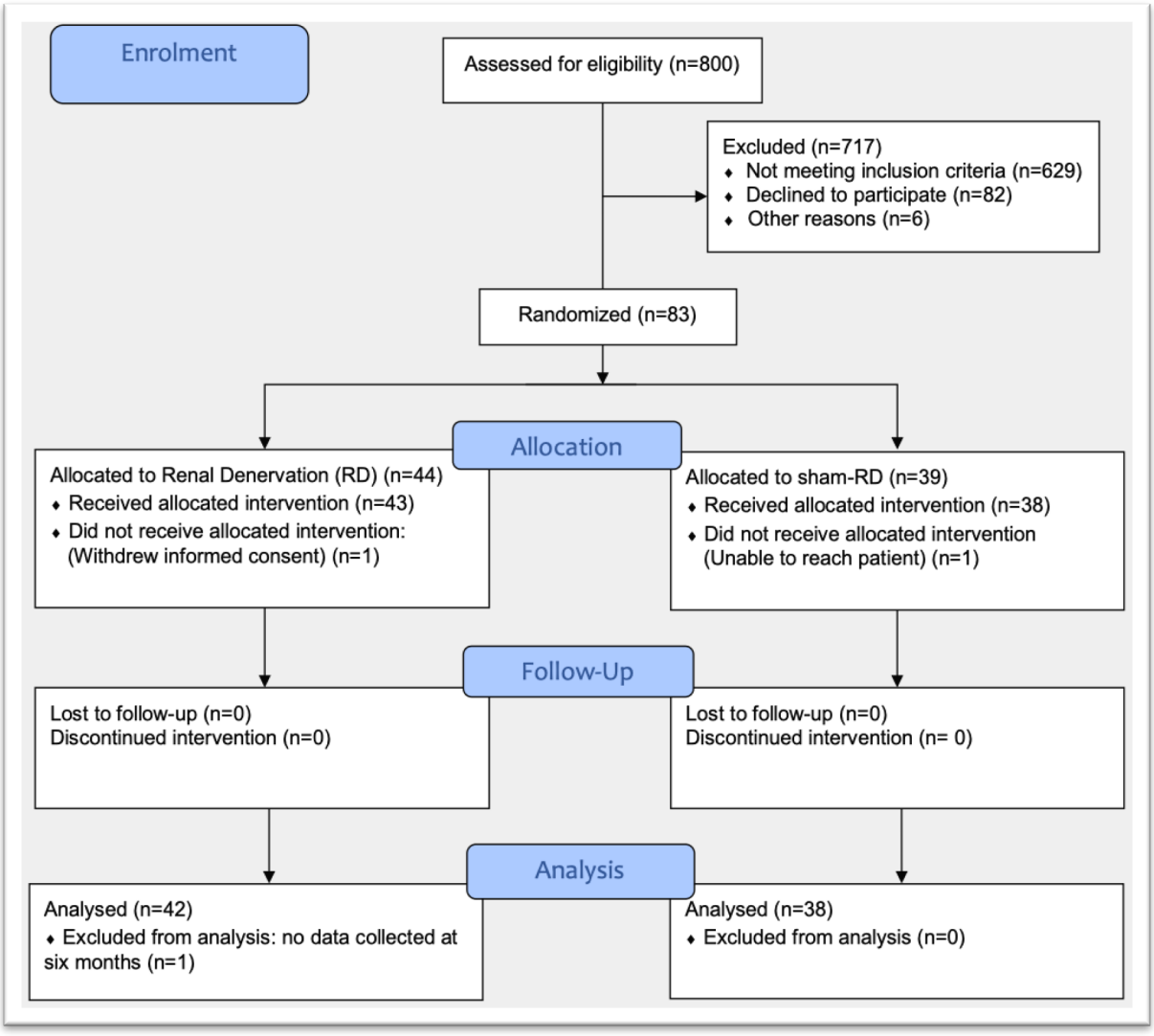


Figure 8. Recruitment, randomisation, follow-up and analysis of data of patients recruited for the study. Although 39 patients were allocated to sham-RD treatment, one patient could not be reached for admission for the procedure, resulting in 38 analysed in the sham arm.

Baseline characteristics

Baseline characteristics were similar across the study groups (Table 1). Participants with male sex were more prevalent in both groups. Most of the subjects were obese (BMI > 30 kg/m^2) with a central obesity distribution. Participants with white race were more prevalent (56%), followed by mixed race patients. (41%). Blacks were under-represented in the study (3% of the study population).

More than half of the population (56%) were diagnosed with obstructive sleep apnoea and 16% had previous strokes/transient ischemic attacks. Peripheral arterial disease was prevalent in 11% of the total study population. Type 2 diabetes mellitus prevalence was 54%; 88% of the study cohort took statins and 13% were current smokers.

Overall, 28% of the patients reported previous episodes of AF. The CHA_2DS_2-VASc score, which is used to assess which patients should be treated with oral anti-coagulation when they develop AF, did not differ between groups and at baseline; 12% of the study population were prescribed an oral anti-coagulant (warfarin or novel oral anti-coagulant) by their treating physicians.

Coronary artery disease (CAD), confirmed during coronary angiography, was prevalent in 68% of patients and 26% of patients had previous myocardial infarctions. Triple vessel CAD was present in 24% of the overall cohort and the European Heart SCORE did not differ significantly between groups (Table 2). None of the patients had an acute coronary syndrome the day before or on the day of coronary angiography.

Table 1. Baseline Characteristics of the Study Population. *

Characteristic	RD Group (n = 42)	Sham Group (n = 38)	P-VALUE
Age (yrs)	65.2 ± 6.9	66.0 ± 8.2	0.637
Male sex-no. (%)	29 (69)	30 (79)	0.446
Abdominal girth (cm)	115.6 ± 11.3	116.2 ± 12.7	0.824
Body mass index (kg/m^2) #	34.7 ± 6.2	33.3 ± 6.3	0.320
Race no. /total no. (%) $			
Black	1 (2)	1 (3)	1.000
White	24 (57)	21(55)	1.000
Mixed Race	17 (40)	16 (42)	1.000
Medical history-no. (%)			
Previous atrial fibrillation	13 (31)	9 (24)	0.617
Obstructive sleep apnoea	24 (57)	21 (55)	1.000
Stroke/Transient ischemic attack	6 (14)	7(18)	0.764
Peripheral arterial disease	6 (14)	3 (9)	0.487
Coronary artery disease	28 (67)	26 (68)	1.000
Myocardial infarction	12 (29)	9 (24)	0.800
Diabetes Type 2	25 (60)	18 (47)	0.370
Hyperlipidemia-no. (%)	36 (86)	34 (89)	0.741
Current smoker-no. (%)	4 (10)	6 (16)	0.506
CHADS-VASC Score	2.81 ± 1.11	2.66 ± 1.12	0.546
Oral anticoagulation (VKA or NOAC)-no. (%)	6 (14)	4 (11)	0.741

***: Plus-minus values are means ± SD. All differences in characteristics between groups were non-significant.**
#: The body mass index is the weight in kilograms divided by the square of the height in meters.
$: Race was determined by self-report.

Table 1 (continued). Baseline Characteristics of the Study Population. *

	RD Group (n = 42)	Sham Group (n = 38)	P-VALUE
Office systolic blood pressure (mmHg)	149.9 ± 20.6	146.3 ± 22.2	0.454
Resting pulse rate (beats/min)	65.59 ± 11.54	64.47 ± 11.00	0.667
Blood pressure medication			
No. of antihypertensive medications	3.57 ± 0.91	3.89 ± 1.11	0.161
ACE-inhibitor -no. (%)	27 (64)	24 (63)	1.000
Angiotensin-receptor blocker-no. (%)	15 (36)	14 (37)	1.000
Aldosterone antagonist -no. (%)	10 (24)	11 (29)	0.621
Direct acting vasodilator (alpha-blocker) -no. (%)	5 (12)	10 (26)	0.151
Beta-blocker-no. (%)	34 (81)	29 (76)	0.785
Calcium channel blocker -no. (%)	19 (45)	23 (61)	0.187
Diuretic, other than AA -no. (%)	39 (93)	36 (95)	1.000
Transthoracic echocardiogram			
Left ventricular ejection fraction (%)	63.4 ± 8	64.7 ± 9	0.496
Left atrial dimension (mm)	46.0 ± 4.6	46.1 ± 4.4	0.921
Left atrial volume index (ml/m^2)	41.4 ± 13.2	43.6 ± 11.4	0.430
Left ventricular mass (grams)	247.9 ± 65.7	278.3 ± 71.2	0.051[&]
Left ventricular hypertrophy (LVH) on echo: no. [&] (Males: LVMI >115g/m^2; females: LVMI>95g/m^2	20 (48)	26 (68)	0.073[&]
E/e' ratio	11.5 ± 4.2	12.9 ± 6.8	0.266

ACE denotes angiotensin-converting enzyme.
[&]: LV mass and LVH prevalence showed a trend to be higher in the Sham-group.

Table 2. Baseline coronary artery disease involvement and European SCORE calculation.			
	RD treated (n=42)	Sham RD treated (n=38)	p-value
Single vessel CAD-no. (%)	7 (7)	4 (11)	0,53
Double vessel CAD-no. (%)	10 (24)	10 (27)	0,80
Triple vessel CAD- no. (%)	10 (24)	10 (27)	0,80
European SCORE count	6,35±5,13	4,9±2,53	0,16

Office blood pressure and anti-hypertensive treatment

Baseline office systolic blood pressure was 147.5 ± 21.2 mmHg for the study population and did not differ between groups (RD: 149.9 ± 20.6 mmHg vs 146.3 ± 22.2 mmHg; p = 0.454). Although 22 of 80 patients (28%) had an office SBP < 140 mmHg, 37 ± 27% of their ambulatory SBP measurements were > 140 mmHg, confirming the diagnosis of baseline uncontrolled HT. The average number of anti-hypertensive drugs (RD: 3.57 ± 0.91 vs sham: 3.89 ± 1.11; p = 0.161) and drug class were not different. ACE-inhibitors were more frequently prescribed than angiotensin-receptor blockers. Beta blockers were more frequently prescribed than calcium channel blockers. Spironolactone was prescribed to 26% of the overall study population.

Echocardiogram dimensions

LV ejection fraction, LA dimension or LAVI did not differ between groups. LV mass was heavier (30 g) in the sham compared to RD group (p = 0.051). LVH was non-significantly more prevalent in the sham group (68% vs 48%; p = 0.073), but the non-invasive marker of diastolic dysfunction, the E/e' ratio, did not differ between groups.

Procedural details

Overall, ten patients (12.5%) were revascularized: three patients in each group received intra-coronary stents in and two patients in each group were referred for bypass surgery. In four patients (9.5%) RD was performed via brachial or radial artery puncture, the rest was treated femorally. Two of 42 patients (4.8%) had accessory renal arteries that were ablated during the same procedure. RD patients underwent 24 ± 9 ablations during 26 ± 9.7 minutes and on average, 16 ablations were safely performed in the branch arteries after the renal artery bifurcation.

Primary endpoint: Subclinical Atrial Fibrillation (SAF)

After three years average follow-up, fewer RD patients experienced SAF: 6 of 42 RD patients (14.3%) vs 15 of 38 (39.5%) sham patients (odds ratio [OR], 0.256, 95% confidence interval (CI), 0.087–0.754; p = 0.012) (Figure 9).

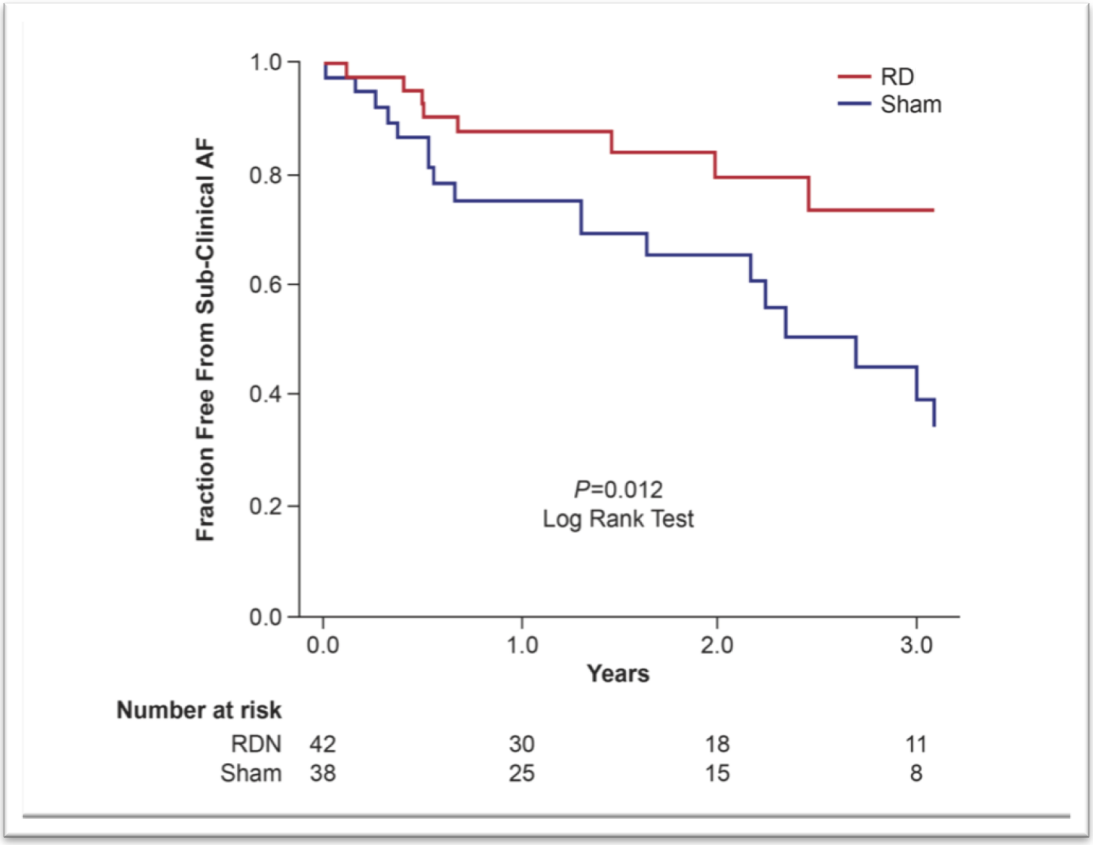


Figure 9. Cumulative incidence of subclinical atrial fibrillation. Patients with hypertensive heart disease were randomised to renal denervation (RD) or a sham-RD procedure.

The absolute SAF risk reduction was 25.2% and four patients had to be treated with RD to prevent one SAF event. SAF relative risk was reduced by 64% with RD compared to the sham RD procedure (Figure 10).

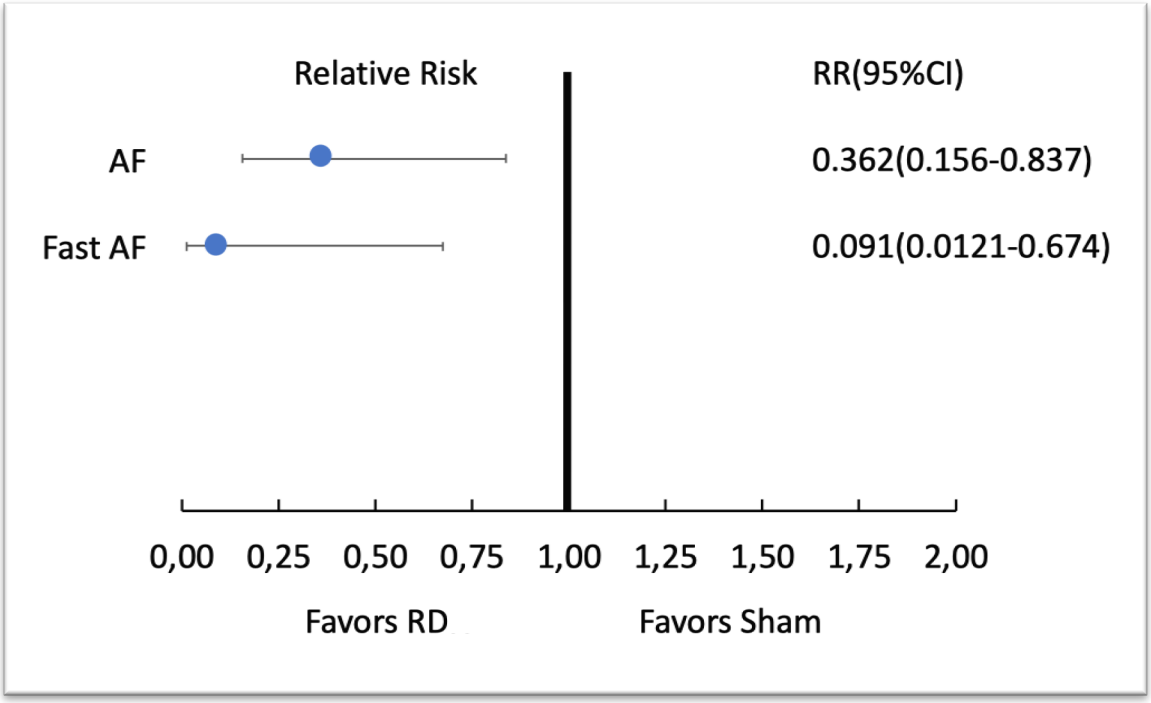


Figure 10. Relative risk of atrial fibrillation (AF) in hypertensive heart disease patients who underwent renal denervation (RD) or a sham procedure.

Fast AF, defined as a ventricular rate of ≥ 100 bpm on the 12 lead ECG or implantable loop recorder, was significantly more prevalent in the sham group (10 of 38 (26.3%) vs 1 of 42 (2.4%); OR, 14.64; 95% CI, 1.77–120.91; p = 0.002). Compared to patients who underwent a sham RD procedure, the relative risk to experience fast AF after RD was reduced by 91%. Every patient with fast AF were considered to be in "clinical AF" and were symptomatic and admitted for urgent cardioversion. Stratification for prior AF and its recurrence was not performed because not every subject have reached the three year follow up point yet.

SECONDARY ENDPOINTS

Office blood pressure

Systolic office blood pressure (SBP) between groups did not differ at baseline but was significantly reduced at 6MFU in patients randomised to RD (148.76 ± 20.42 mmHg to 136.37 ± 16.91 mmHg: −12.88 ± 20.64 mmHg reduction; p = 0.0003). There was also a trend of SBP reduction in sham subjects (−9.13 ± 25.22 mmHg reduction; p = 0.053). The between-group difference did not differ significantly: –3.8 mmHg; p = 0.49 (Figure 11).

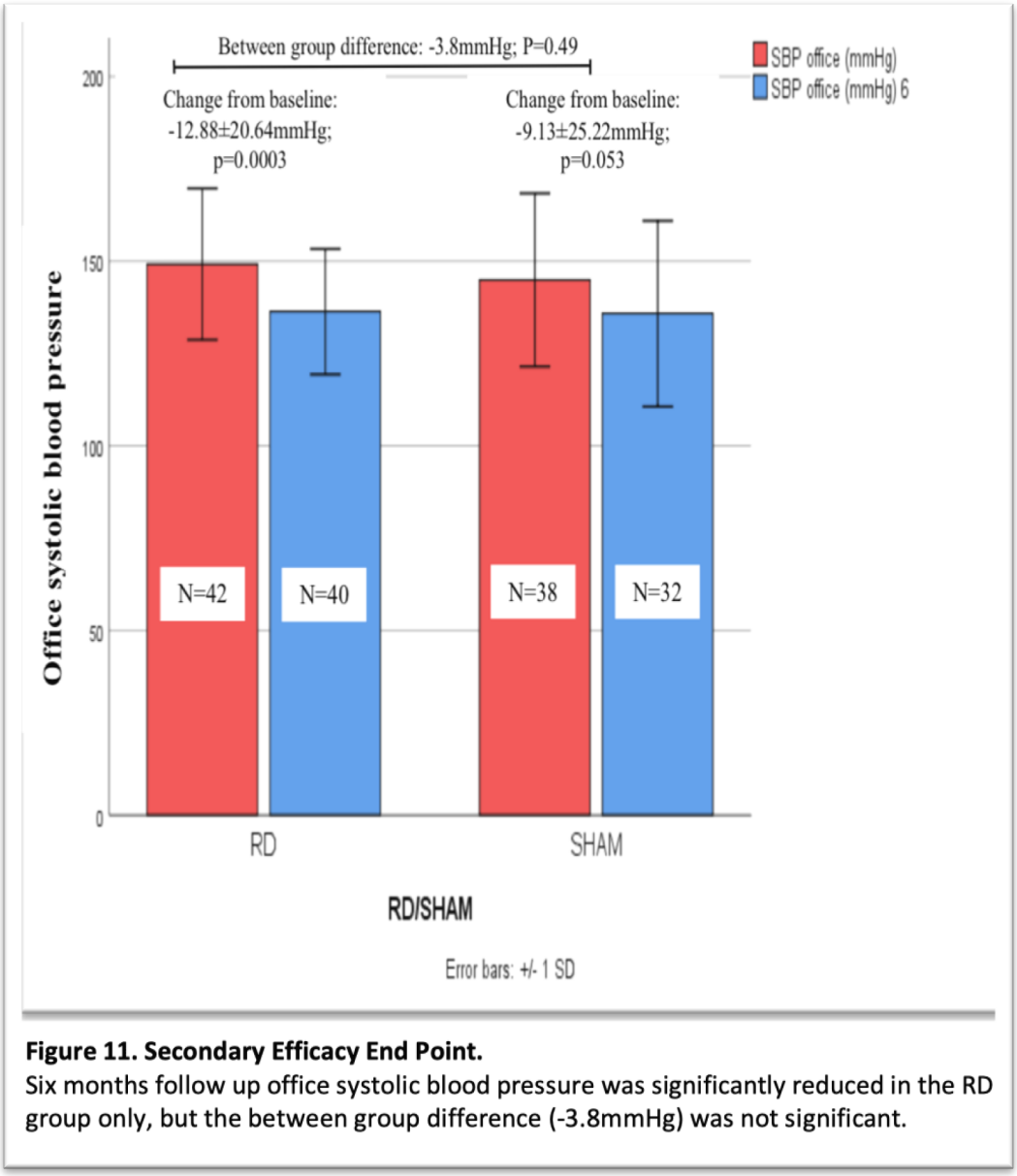


Figure 11. Secondary Efficacy End Point.
Six months follow up office systolic blood pressure was significantly reduced in the RD group only, but the between group difference (-3.8mmHg) was not significant.

Similarly, office diastolic blood pressure (DBP) was significantly reduced following RD (−6.2 mmHg; p = 0.003), but not in the sham group (−3.9 mmHg; p = 0.17). The between-group 6-month DBP difference of −2.3 mmHg was not significant (p = 0.49).

24hr-Ambulatory blood pressure

All variables included in this analysis were normally distributed. Thirty-four ambulatory BP measurements could be analysed: 20 in the RD group (48%) and 14 in the sham group (37%) (Table 3). This implied that more than half of the study population (57%) had either uninterpretable or absent ABPM measurements. ABPM measurements did not differ between groups at baseline. The baseline prevalence of isolated systolic hypertension was 20% in RD patients and 14% in sham patients, respectively (p = 1.00).

Table 3. Ambulatory blood pressure: RD vs sham.
Baseline and 6 months follow-up ambulatory blood pressure measurements (ABPM). The ABPM was considered valid if it recorded at least 33 successful measurements.

	Sham		RD		p-value
	Value	N	Value	N	
Baseline					
Mean 24h-SBP, mmHg	149.1 ± 19.5	14	146.1 ± 19.4	20	0.67
Minimum 24h-SBP, mmHg	103.4 ± 17.1	14	98.4 ± 22.2	20	0.48
Maximum 24h-SBP, mmHg	200.1 ± 29.8	14	203.5 ± 27.6	20	0.74
Daytime mean SBP, mmHg	150.9 ± 18.5	14	147.8 ± 19.1	20	0.64
Nighttime mean SBP, mmHg	139.4 ± 24.4	14	135.4 ± 25.0	19	0.65
Mean 24h-DBP, mmHg	84.0 ± 9.1	14	80.6 ± 9.9	20	0.31
Minimum 24h-DBP, mmHg	49.1 ± 9.6	14	48.0 ± 6.7	20	0.70
Maximum 24h-DBP, mmHg	134.6 ± 22.5	14	136.6 ± 21.0	20	0.79
Mean daytime DBP, mmHg	84.6 ± 6.9	11	81.1 ± 9.6	18	0.30
Mean nighttime DBP, mmHg	78.3 ± 10.4	11	71.3 ± 12.0	17	0.13
Mean 24h-pulse rate, bpm	65.6 ± 10.1	13	67.8 ± 7.6	20	0.48
Mean day time pulse rate, bpm	66.0 ± 10.3	11	68.0 ± 7.7	18	0.55
Mean night time pulse rate, bpm	62.7 ± 10.2	11	62.8 ± 8.1	17	0.98
Isolated systolic hypertension*, No. (%)	2 (14)	14	4 (20)	29	1.00
6 months follow up					
Mean 24h-SBP, mmHg	141.8 ± 15.2	14	143.0 ± 12.6	20	0.80
Minimum 24h-SBP, mmHg	101.3 ± 14.1	12	98.9 ± 15.0	20	0.66
Maximum 24h-SBP, mmHg	194.1 ± 27.2	14	206.3 ± 30.7	20	0.24
Daytime mean SBP, mmHg	144.0 ± 14.8	14	144.8 ± 12.7	20	0.86
Nighttime mean SBP, mmHg	131.4 ± 19.1	14	135.9 ± 17.0	20	0.48

The change in ambulatory SBP did not differ within or between the groups (-4.1mmHg; p = 0.36) (Figure 12).

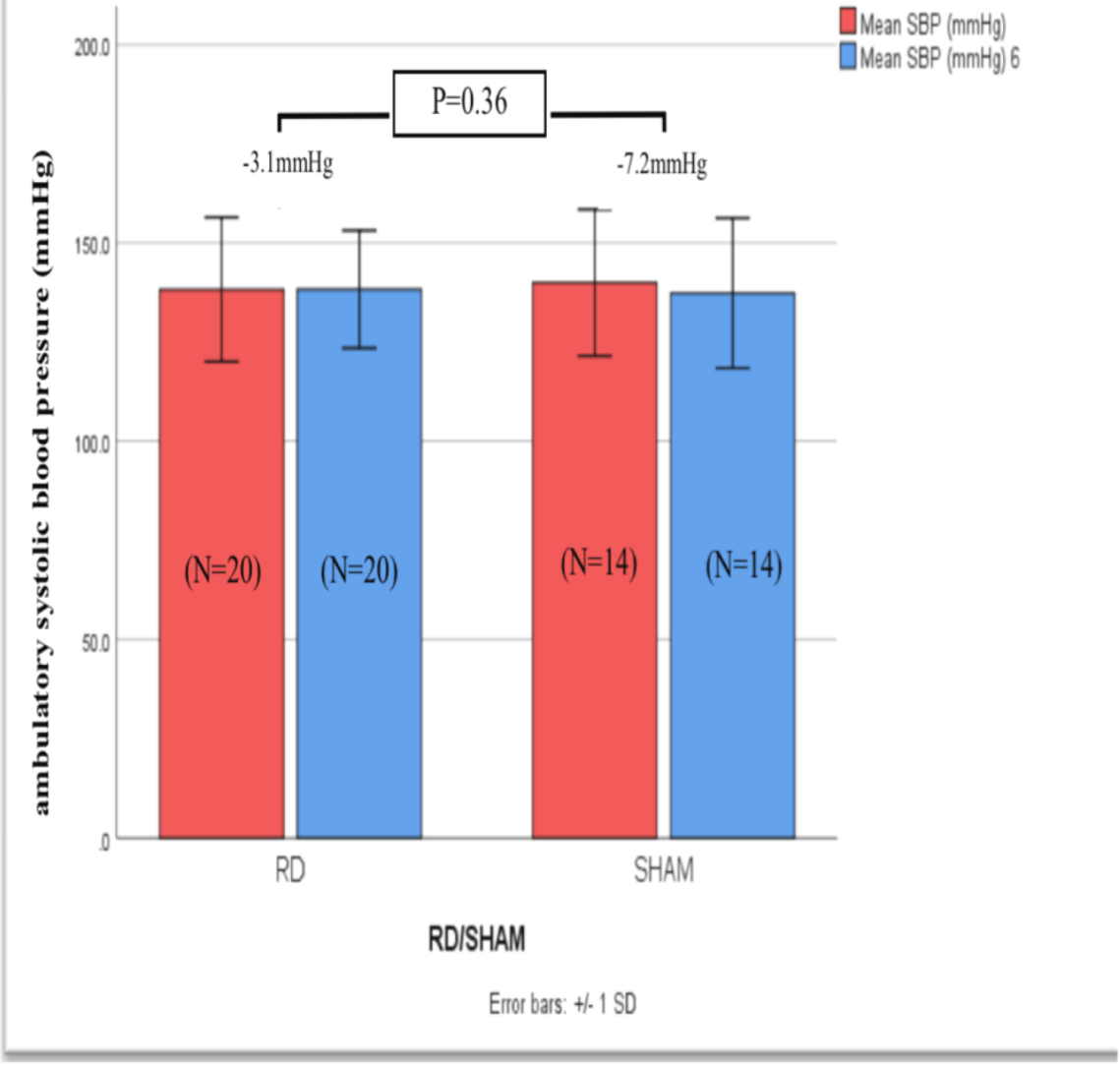


Figure 12. Mean ambulatory systolic blood pressure (SBP).
Six months follow up ambulatory systolic blood pressure did not change significantly within or between groups.

Cardiovascular death

At an average of three years follow-up, cardiovascular death incidence was significantly lower in the RD group compared to sham RD (1 of 42 [2.4%] vs 6 of 38 [15.8%]: OR, 0.13, 95% CI, 0.01–1.14; p = 0.049 (Figure 13).

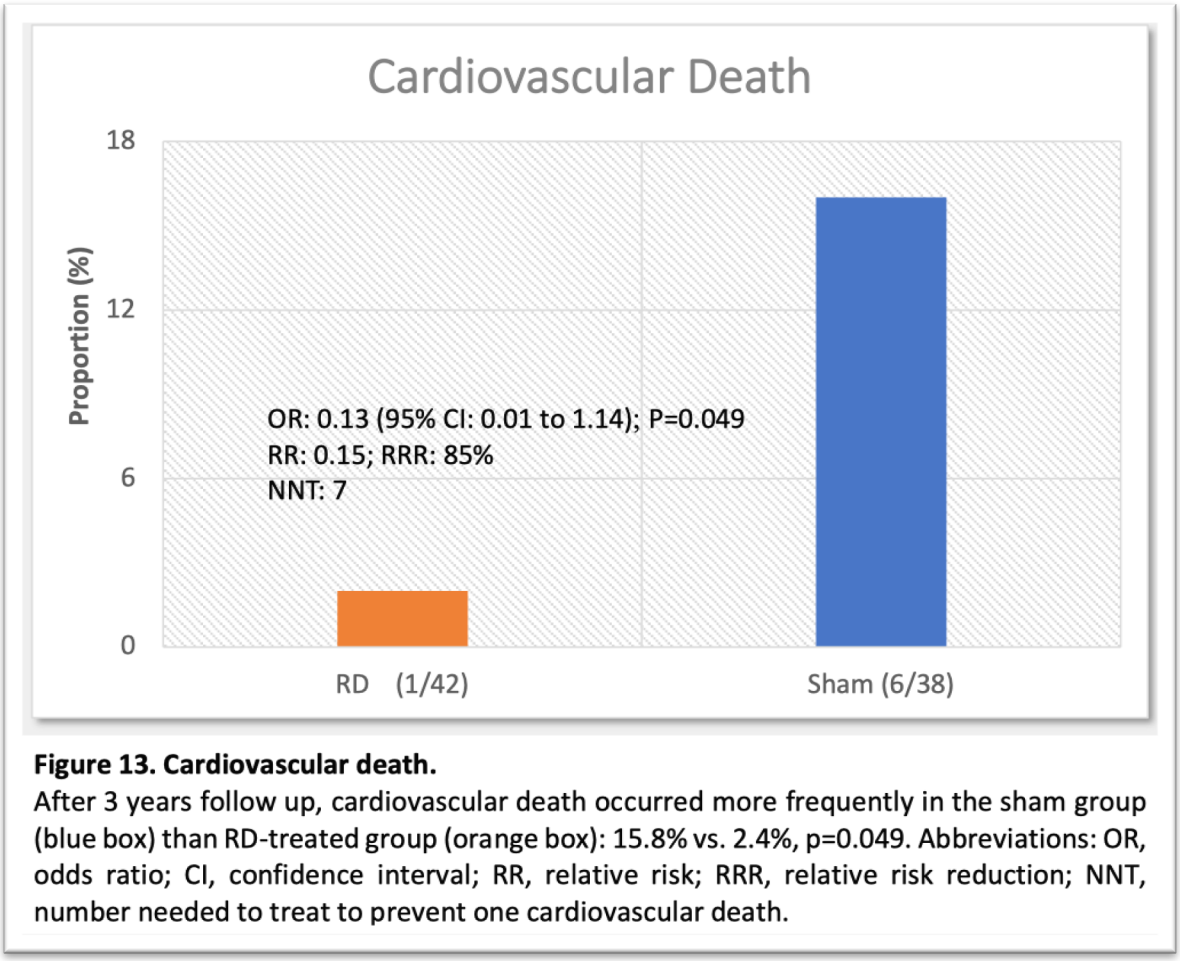


Figure 13. Cardiovascular death.
After 3 years follow up, cardiovascular death occurred more frequently in the sham group (blue box) than RD-treated group (orange box): 15.8% vs. 2.4%, p=0.049. Abbreviations: OR, odds ratio; CI, confidence interval; RR, relative risk; RRR, relative risk reduction; NNT, number needed to treat to prevent one cardiovascular death.

The relative risk of cardiovascular death was non-significantly reduced by RD with 85% (RR, 0.15, 95% CI, 0.02–1.20) and seven patients needed to be treated with RD to prevent one cardiovascular death.

Chest pain syndromes

Unstable angina

During follow-up, 23 of the 80 study patients (29%) experienced an acute coronary syndrome (ACS) requiring hospital admission (Table 4). Fourteen patients had unstable angina with persistently negative cardiac troponins: five (12%) in the RD group and nine (24%) in the sham group. The incidence of unstable angina did not differ between groups (OR, 0.43; 95% CI, 0.13–1.44; p = 0.24).

Table 4. Incidence of pre-specified, secondary cardiovascular endpoints in patients randomised to renal denervation (RD) or a sham procedure. NSTEMI denotes non-ST elevation myocardial infarction and STEMI denotes ST-elevation myocardial infarction. "*", defines significant p-value.

Cardiovascular Event	RD (n = 42)	Sham (n = 38)	Odds ratio	95% CI	p-value
Chest pain syndromes					
Unstable angina: no. (%)	5 (12)	9 (24)	0.43	0.13-1.44	0.24
NSTEMI: no. (%)	1 (2.3)	7 (18.4)	0.11	0.01-0.92	0.02*
STEMI: no. (%)	0 (0)	1 (2.6)	0.29	-	0.47
Pulmonary embolism: no. (%)	1 (2.4)	1 (2.6)	0.90	0.05-14.95	1.00
Stroke/transient ischemic attack					
Incidence: no. (%)	4 (9.5)	1 (2.6)	3.89	0.42-36.50	0.36

Myocardial infarction (NSTEMI and STEMI)

Eight patients had positive cardiac troponins without ST-segment elevation (NSTEMI) prior to coronary angiography: one in the RD group (2.3%) vs seven in the sham group (18.4%) (OR, 0.11; 95% CI, 0.01–0.92; p = 0.02. Compared to sham treatment, the relative risk to experience an NSTEMI after RD was 0.129 (95% CI, 0.02–1.00). One patient in the sham group (2,6%) and none in the RD group (0%) experienced an ST-elevation myocardial infarction (p = 0.47).

Pulmonary embolism

One patient in each group had a non-fatal pulmonary embolism: 1 of 42 patients (2.4%) in the RD group and 1 of 38 (2.6%) in the sham group (OR, 0.9; 95% CI, 0.05–14.94; p = 1.00). Both were older men with permanent pacemakers and a history of previous deep venous thrombosis. Both patients were started on warfarin aiming for a therapeutic INR of 2–3. They did not experience any further complications.

Neurological events

During follow-up, five transient ischemic attacks occurred in four RD patients (9.5%) and one sham patient (2.6%), respectively (OR, 3.89; 95% CI, 0.42–36.50; p = 0.36). None of these patients had an intracranial haemorrhage or signs of raised intracranial pressure on their admission CT brain scan. They were not treated with intravenous thrombolytic drugs, but their neurological signs disappeared completely within 24 hours. These events were thus regarded as “embolic” and patients with SAF on their ILR, were started on life-long warfarin, if there were no contra-indications to anti-coagulation. Patients without ILR SAF were treated

with dual-anti-platelet therapy for six months, after which clopidogrel was discontinued and aspirin continued for life.

Echocardiographic parameters that may be influenced by RD

6MFU echocardiographic data were available for 68 of 80 patients (85% of total population) including 38 patients in the RD group and 30 patients in the sham group (Table 5).

Table 5. Between-group difference of pre-specified echocardiographic parameters at six months follow up.

ECHO PARAMETER	RENAL DENERVATION (RD): CHANGE AT SIX MONTHS FOLLOW UP	SHAM RD: CHANGE AT SIX MONTHS FOLLOW UP	BETWEEN GROUP DIFFERENCE (95% CI)	P-VALUE
LV EJECTION FRACTION (%)	+ 0.66 ± 5.78 (n=38)	+ 0.23 ± 7.98 (n=30)	0.43 (-2.9 to 3.76)	0.80
LV MASS (grams)	-4.30 ± 48.73 (n=37)	-8.94 ± 59.10 (n=33)	4.64 (-30.37 to 21.09)	0.72
LV MASS INDEX (g/m^2)	-0.66 ±25.26 (n=37)	-4.78 ± 25.00 (n=32)	4.12 (-16.23 to 7.99)	0.50
LEFT ATRIAL DIMENSION (mm)	-0.76 ± 2.72 (n=38)	-0.34 ± 2.40 (n=32)	0.42 (-1.65 to 0.81)	0.50
LEFT ATRIAL VOLUME INDEX (LAVI) (ml/m^2)	-1.19 ± 13.72 (n=21)	-2.13 ± 12.46 (n=16)	0.94 (-9.83 to 7.95)	0.83

LV ejection fraction

Baseline LV ejection fraction (LVEF) did not differ between groups (Table 1). At 6MFU, 38 RD patients experienced a nonsignificant LVEF increase of 0.66 ± 5.78% vs 0.23 ± 7.98% increase in 30 sham patients (p = 0.80).

LV mass/LV mass index

At baseline, LV mass was heavier and LVH significantly more prevalent in the sham than RD group (Table 1). At 6MFU, LV mass (LVM) decreased non-significantly in both groups, but more in the sham group: RD: −4.30 ± 48.73 g vs sham: −8.94 ± 59.10 g; p = 0.72. More than half of the patients in each cohort experienced a reduction in LVM: 19 of 37 RD patients (51%) vs 19 of 33 sham patients (58%); p = 0.64. LV mass index (LVMI) was also non-significantly reduced in both groups (p = 0.50), but more in the sham group.

Left atrial dimension/volume index

At 6MFU, left atrial (LA) dimension was non-significantly reduced in both groups: RD: −0.76 ± 2.72 mm vs sham: −0.34 ± 2.40 mm; p = 0.50. More RD patients experienced a reduction in LA dimension at 6MFU: 16 of 38 RD patients (42%) vs 11 of 32 sham patients (34%); p = 0.62. LA volume index (LAVI) decreased non-significantly in both groups (p = 0.83).

E/e': A marker of diastolic dysfunction

E/e' values had a skewed distribution and data were analysed using a Mann-Whitney U test. E/e' was non-significantly reduced in both groups (Figure 14). The between-group differences did not differ significantly (p = 0.71). The prevalence of diastolic dysfunction, defined as E/e' > 14 also did not differ between groups at baseline or 6MFU.

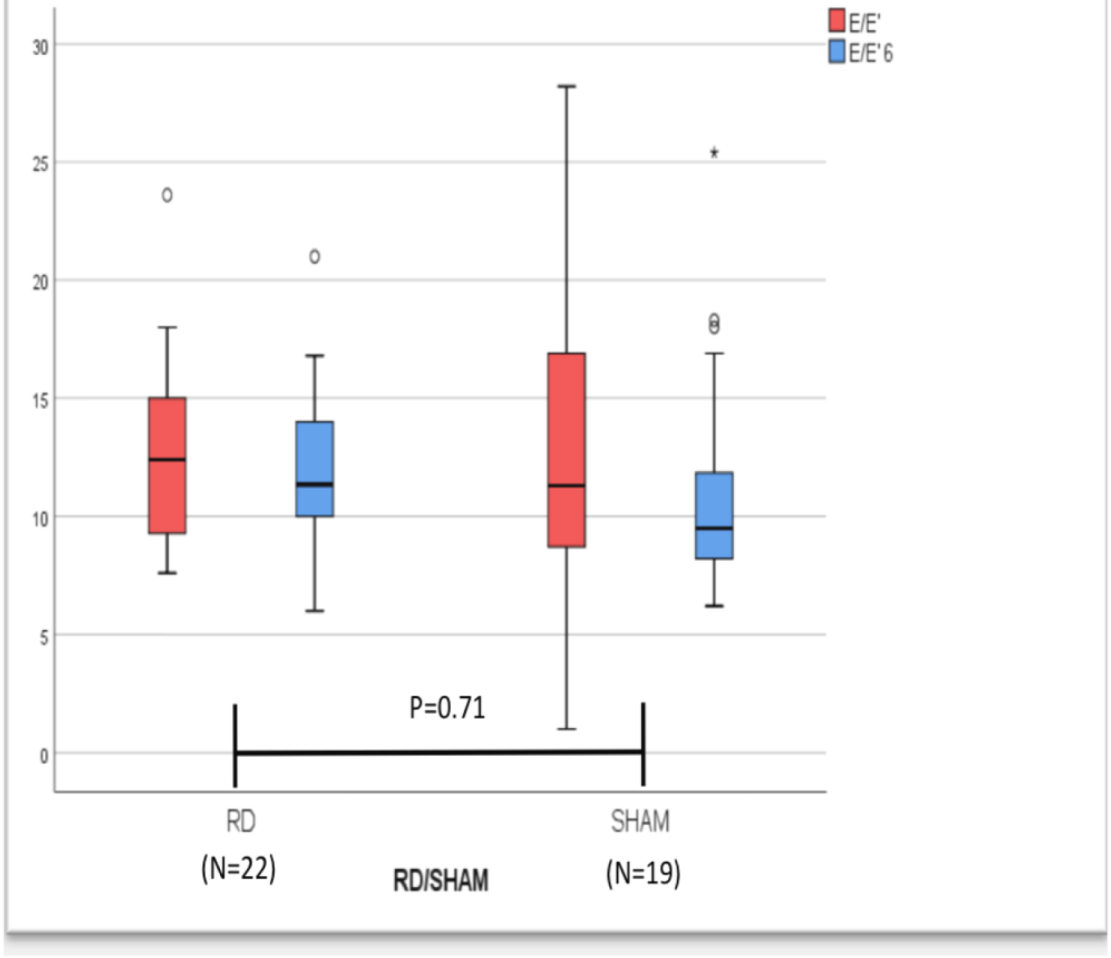


Figure 14. E/e', a unitless echocardiographic marker of diastolic dysfunction.

Box and whisker plots with median and interquartile ranges. RD denotes renal denervation. The red boxes represent baseline values and the blue boxes represent 6 months follow up (6MFU) values. E/e' was non-significantly reduced in both groups.

Cardio-autonomic markers

Resting heart rate (RHR)

Resting ECG data of 41 RD and 36 sham patients, respectively, were analysed at baseline (Table 9). Baseline resting heart rate (RHR) did not differ between groups. After 6MFU, complete data were available for 38 RD and 28 sham patients, respectively (Table 6).

Table 6. Baseline and 6 months follow up ECG-parameters that may be used as surrogate markers of cardio-autonomic tone. P-values were calculated with non-paired student t-tests.

ECG parameter	RD	N	Sham	N	P-value
BASELINE					
Resting heart rate (RHR) (bpm)	65.59 ± 11.54	41	64.47 ± 11.00	36	0.67
24hr ambulatory heart rate (AHR) (bpm)	67.78 ± 9.54	41	66.39 ± 9.26	33	0.53
Heart rate recovery (peak exercise heart rate minus one-minute recovery heart rate)	22.66 ±12.46	38	25.35 ±11.67	31	0.36
6 MONTHS FOLLOW UP					
Resting heart rate (RHR) (bpm)	64.34 ± 11.10	38	64.46 ± 10.25	28	0.96
24hr ambulatory heart rate (AHR) (bpm)	67.92 ± 8.55	36	68.15 ± 9.88	34	0.92
Heart rate recovery (peak exercise heart rate minus one-minute recovery heart rate)	23.61 ± 12.77	31	26.04 ± 9.51	23	0.45

At 6MFU, RHR did not differ between groups (p = 0.96). More RD patients experienced a reduction in RHR at 6MFU compared to sham patients: 22 of 38 RD patients (59%) vs 10 of 28 sham patients (36%); p = 0,0871. Contrary to RD patients, who had a mild reduction in RHR, sham patients experienced an increase in RHR (Figure 15).

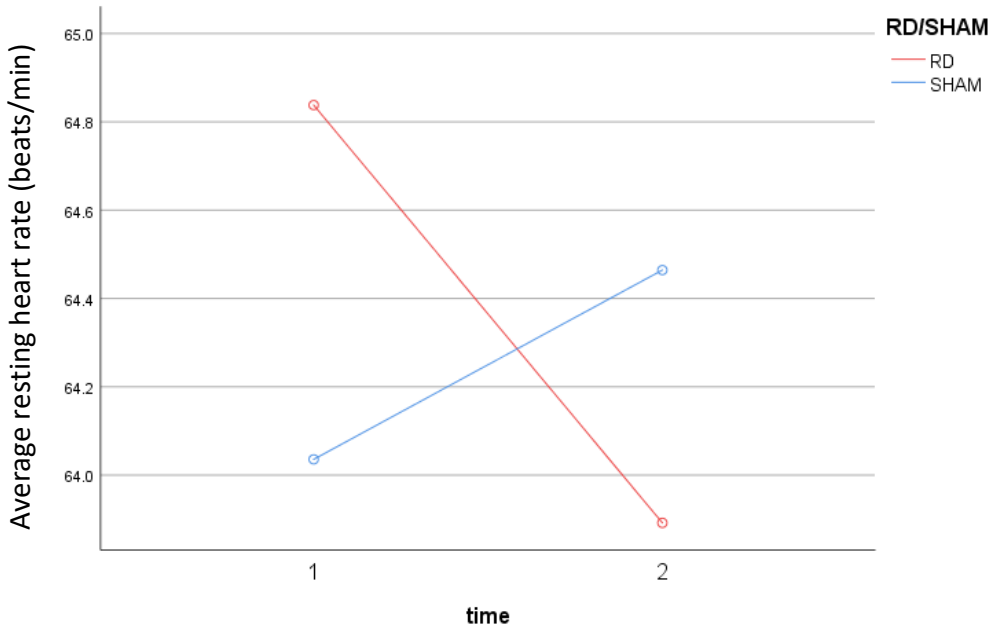


Figure 15. Change in resting heart rate (RHR). Time 1 represents baseline and time 2 represents six months follow up.

24hr holter ECG Ambulatory heart rate

Ambulatory heart rate (AHR) did not differ between groups at baseline (p = 0.53) or 6MFU (p = 0.92) (Table 9). Although average 6MFU AHR was reduced in the RD group (n = 35) and increased in the sham group (n = 30), the between-group difference was not significant (p = 0.36). Contrary to RD patients, sham patients experienced an increase in AHR.

One-minute Heart rate recovery post exercise (HRR)

One-minute HRR did not differ between groups at baseline (p = 0.36) or 6MFU (p = 0.45), respectively. HRR increased in RD patients (n = 28) and decreased in sham patients (n = 22), but did not change significantly between groups over the 6MFU period (delta RD-change: 0.96 ± 16.41 bpm vs delta sham change: −1.64 ± 12.10 bpm; p = 0.54) (Figure 16).

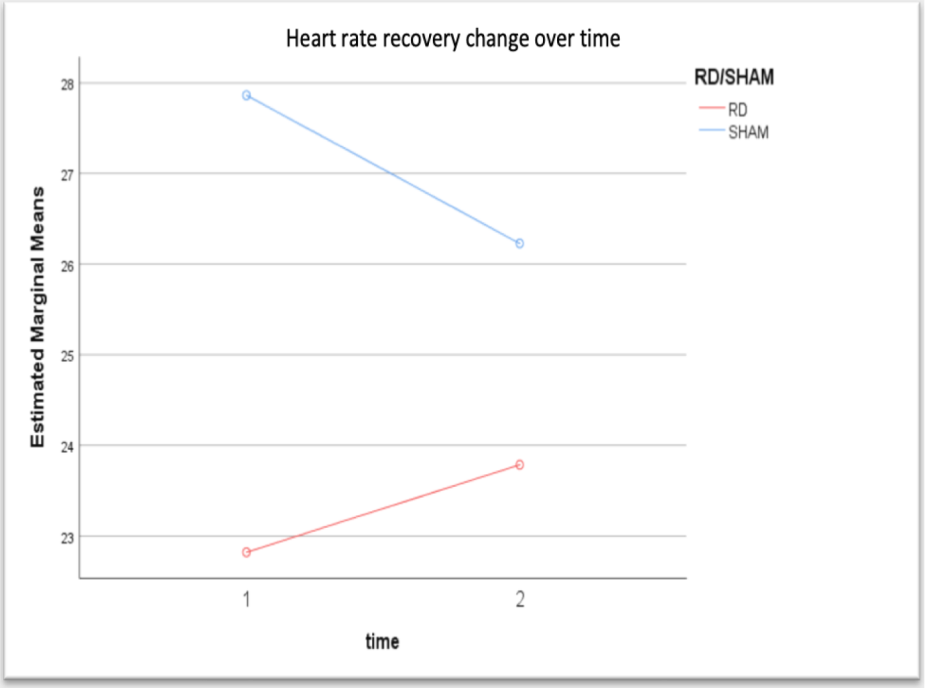


Figure 16. Mean change of heart rate recovery (HRR) over six months of follow up.
Time 1 to time 2. HRR is a surrogate marker of vagal function post-exercise. The red line represents the change over time for RD patients (n=28). The blue line represents the change over time for sham patients (n=22). Circles represent mean HRR at time 1 (baseline) and time 2 (6 months follow up). RD was associated with an increase in mean HRR, whereas mean HRR decreased in sham patients. The between-group change was not significant (p=0.54).

Markers of autonomic imbalance

RHR>75bpm and HRR<25bpm did not differ between groups at baseline at baseline or 6MFU, respectively: (RD: Sham RD; RHR>75bpm at 6MFU: 14% vs 11% ; p= 1.00; HRR<25bpm: RD: Sham RD; 48% vs.39%; p= 0.59).

Heart rate variability: SDNN on 24hr holter ECG

Overall, 49 of 80 patients (61%) had complete time domain HRV/standard deviation of normal to normal intervals (SDNN) measurements at baseline compared to 39 (49%) at 6MFU. Baseline SDNN did not differ between groups (RD: 96.54 ± 25.34 ms [n = 28] vs sham: 104.76 ± 27.88 ms [n = 21]; p = 0.29). Sixteen of 28 RD patients (57%) vs 8 of 21 sham patients (38%) had a reduced SDNN < 100 ms at baseline (p = 0.25). At 6MFU, SDNN increased non-significantly in both groups (p = 0.62) (Figure 17).

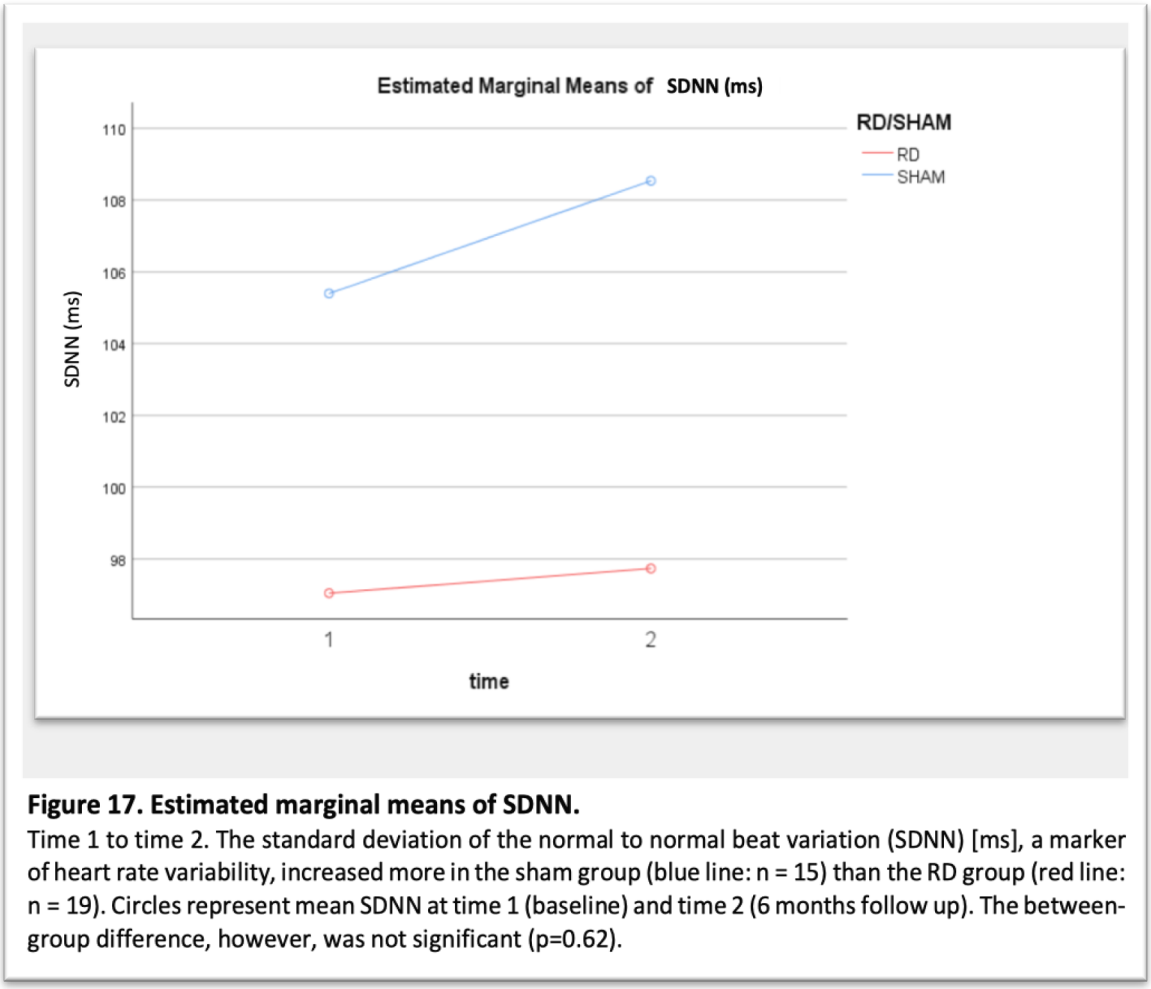


Figure 17. Estimated marginal means of SDNN.
Time 1 to time 2. The standard deviation of the normal to normal beat variation (SDNN) [ms], a marker of heart rate variability, increased more in the sham group (blue line: n = 15) than the RD group (red line: n = 19). Circles represent mean SDNN at time 1 (baseline) and time 2 (6 months follow up). The between-group difference, however, was not significant (p=0.62).

Effect of RD on Cardiac Arrhythmia

Supraventricular ectopy

Supraventricular extrasystoles (SVES) could be assessed in 50 patients at baseline of whom 28 (56%) were randomised to RD. SVES 24 hr-values had had a skewed distribution and ranged from 1/24 hr to > 9000/24 hr at baseline and 0 to > 3000/24 hr at 6MFU, respectively. At 6MFU, SVES could only be assessed in 35 patients of whom 19 underwent RD. RD non-significantly associated with a **trend towards lower SVES burden** (p = 0.056), compared to sham where SVES burden increased at 6MFU (Figure 18).

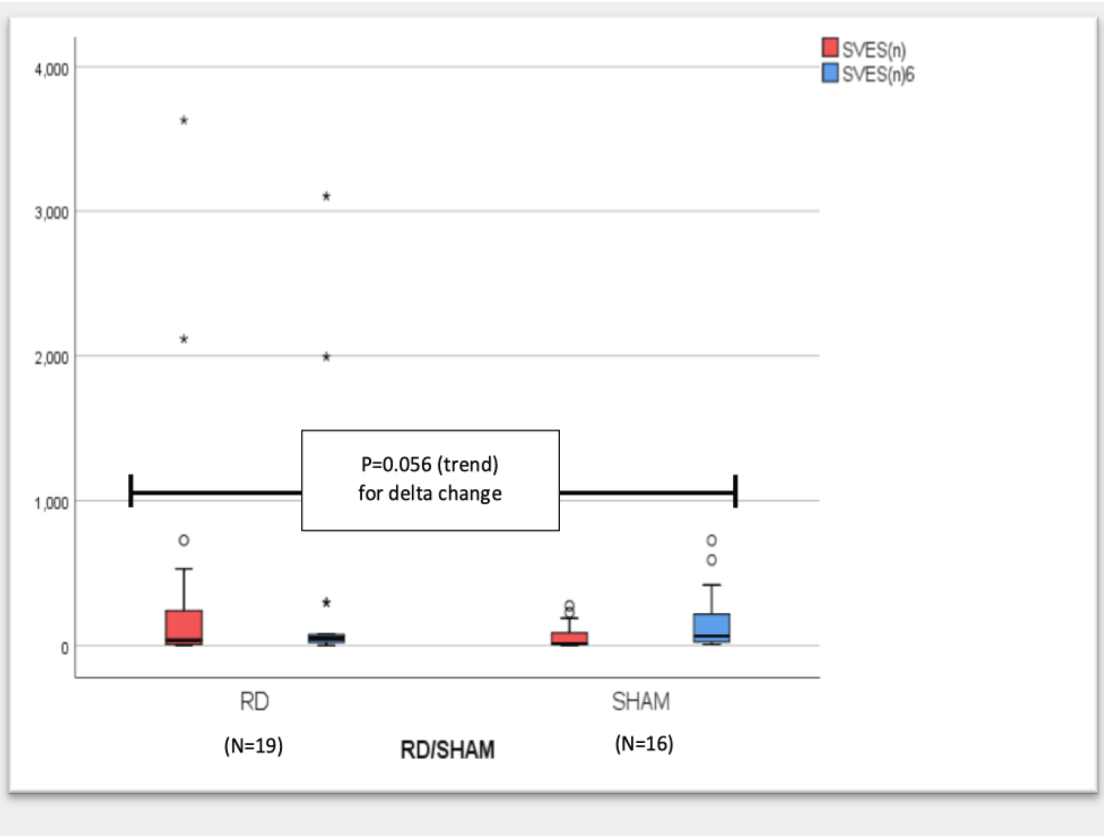


Figure 18. Distribution of supra-ventricular extrasystoles (SVES) detected on a 24hrs holter ECG at baseline and 6 months follow up (6MFU).
Box and whisker plots. Red and blue boxes represent SVES burden at baseline and 6MFU, respectively. RD non-significantly associated with a lower SVES burden, compared to sham where SVES burden increased at 6MFU (p=0.056: trend for delta change).

Ventricular ectopy

Ventricular ectopic beats (VES) were detected in 51 patients at BL and 39 patients at 6MFU, respectively. VES also had a skewed distribution and could not be analysed with parametric tests. The 24 hr values ranged from 0 to > 1400VES/24 hr at baseline and 0 to > 2900/24 hr at 6MFU. Median VEB did not differ between groups at 6MFU (p = 0.99) (Figure 19).

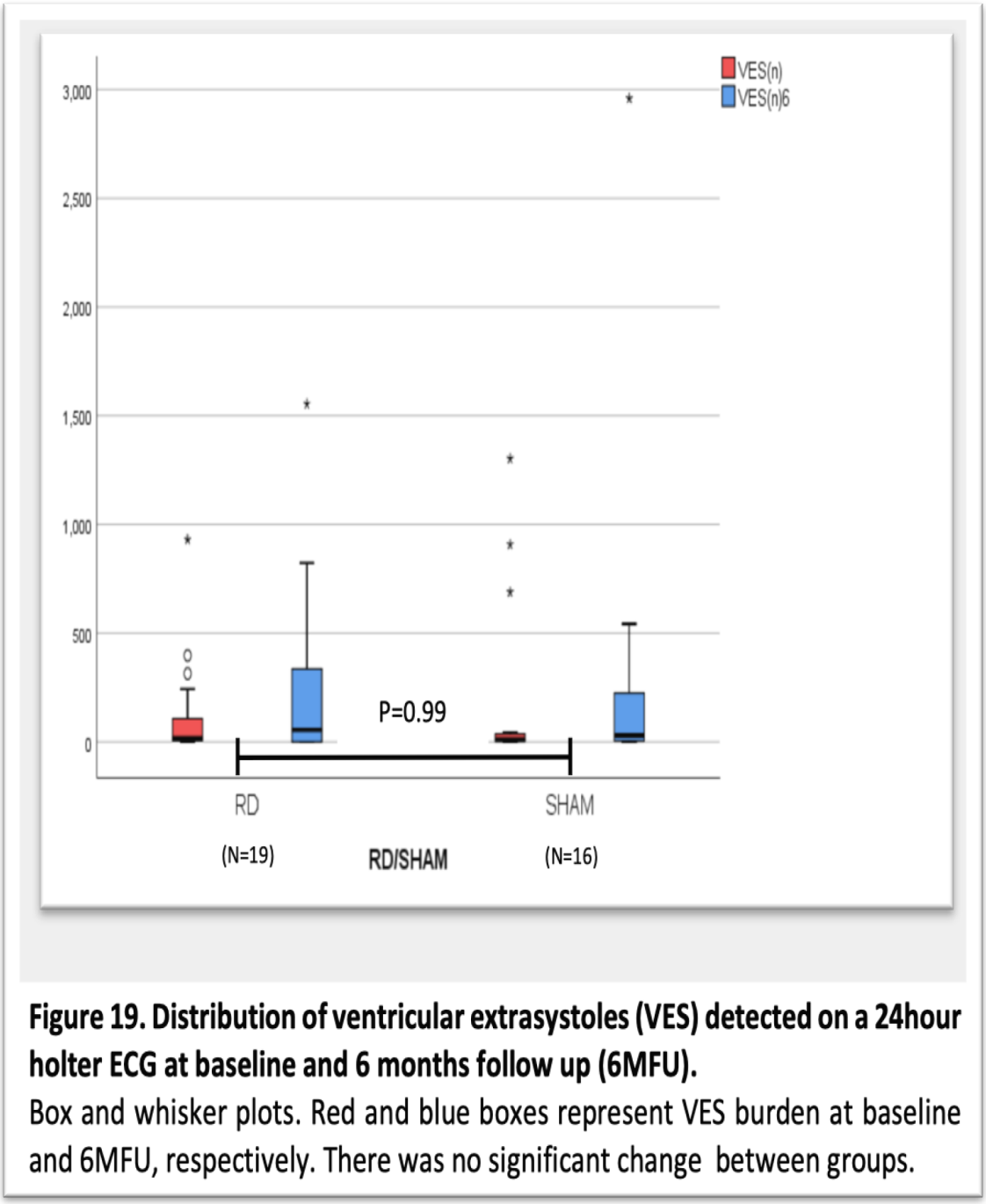


Figure 19. Distribution of ventricular extrasystoles (VES) detected on a 24hour holter ECG at baseline and 6 months follow up (6MFU).
Box and whisker plots. Red and blue boxes represent VES burden at baseline and 6MFU, respectively. There was no significant change between groups.

Effect of RD on QTc-interval

The QTc-interval did not differ between groups at baseline (RD: 433.13 ± 35.39 ms vs sham: 438.14 ± 28.71 ms; p = 0.51) or 6MFU (RD: 433.15 ± 27.50 ms vs sham: 444.56 ± 39.46 ms; p = 0.19).

The prevalence of patients with a prolonged QTc-interval (>440 ms for males and >460 ms for females) did not differ between groups at baseline (14 of 39 RD patients [36%] vs 14 of 35 sham patients [40%]; p = 0.81) or 6MFU (8 of 34 RD patients [24%] vs 7 of 27 sham patients [26%]; p = 1.00).

After 6MFU, QTc was reduced in the RD group, compared to a non-significant increase in the sham group (RD: −3.59 ± 25.68 ms vs sham: 6.52 ± 31.69 ms; p = 0.18).

CHAPTER 4

DISCUSSION

In this single-centre, single-blinded RCT, it was demonstrated that RD reduces subclinical AF and fast AF incidence in patients with HHD, independent of blood pressure lowering. RD treatment was also associated with a reduction in NSTEMI incidence and cardiovascular death. These novel findings have not been reported previously.

Possible mechanisms of the anti-arrhythmic effect associated with RD

The pulmonary veins and left atrium are richly innervated by autonomic nerve fibres.[109] Pre-clinical animal research suggests that RD-induced changes in atrial electrophysiology possibly contributes to the anti-fibrillatory mechanism by reducing atrial nerve sprouting and complexity of AF in goats.[110] Median conduction velocity was higher and AF cycle length was shorter in RDN-AF compared with SHAM-AF. Wang et al. recently showed that RD via renal artery adventitial cryoablation induces fibrosis of the left stellate ganglion nerve fibres. Damage to this vital sympathetic nerve substation significantly reduced novel left atrial sympathetic nerve sprouting and AF inducibility in canines.[111]

Peripheral parasympathetic stimulation may have similar effects. Stavrakis et al. reported that low-level transcutaneous electrical vagus nerve stimulation through a metal clip attached to the ear tragus suppresses AF in humans.[112] These findings support the hypothesis that targeting the autonomic nervous system through peripheral manipulation may provide novel and beneficial anti-arrhythmic effects.[113]

Steinberg et al. recently reported the results of the *ERADICATE-AF* trial, which tested the hypothesis that adding RD to PVI in hypertension-treated patients with PAF will decrease the

recurrence of AF.[114] This multi-centre RCT was conducted in Russia, Poland and Germany and included 305 patients with PAF and hypertension. Baseline characteristics were well-matched, and the mean PAF duration was 3.6 years. PVI was performed with a cryoballoon and successful ablation was confirmed with multi-electrode mapping. The one-year freedom-from-AF rate was significantly higher in patients who underwent additional RD: 72.1% vs 56.5%; HR 0.57; 95% CI 0.38 to 0.85. There were some safety concerns, however: the investigators used standard AF ablation catheters to denervate the renal nerves and not dedicated RD catheters. Major adverse events did not differ significantly between groups. ERADICATE-AF provides further evidence that RD has anti-fibrillatory effects when added to PVI. One of the concerns about this trial is that it was not definitive and carried out in a population with hypertension that was not well-controlled.

The current study is first of its kind to suggest that RD could potentially be used as an upstream or stand-alone therapy to prevent AF in patients with HHD.

RD and autonomic imbalance

None of the proposed markers of cardio-autonomic tone (SDNN and heart rate profiles at rest, during ambulation and exercise) was significantly improved by RD in our study. Several confounders may have influenced these results, however.

First, it is possible that these findings represent a *type II statistical error* underscoring insufficient power to test the proposed hypothesis that RD corrects autonomic imbalance. Second, there are currently *no established normal HRV cut-off values* for this older, obese population who has HHD and CCD. To advance this research field, this study tested the

feasibility of using other heart rate profiles (RHR, 24 hr AHR and HRR) to assess cardio-autonomic tone (CAT). Ukena et al. recently reported that RD was significantly associated with reduced 24 hr ambulatory heart rate in patients with resistant hypertension who had a baseline HR > 72 beats/min.[115] Similar to the current study, they also reported that RD was associated with a reduced supraventricular ectopic burden, but they could also not demonstrate improved HRV. This potentially important finding implies that RD either does not affect HRV, which is primarily under vagal control, or that RD only reduces acute adrenergic surges translating into beneficial anti-fibrillatory effects. Although it was probably sufficiently powered, the Ukena study may have some flaws. In their non-randomised prospective cohort study, patients acted as their own controls. Selection bias and the Hawthorne effect may also have influenced their results. A such, it is important to remember that their reported association does not necessarily prove causality and is subject to confounding.

Finally, the high prevalence of concomitant BB therapy (> 75%) in a population with both HHD and CAD may have influenced the results of CAT testing. In this regard, HRR, which is purely under vagal control, was added to the autonomic tests. An improvement in HRR, albeit non-significantly, reflects an improvement in parasympathetic tone, suggesting that reduced sympathetic tone through RD may indirectly increase inhibitory vagal cardiac reflexes. Larger randomised trails may provide an answer to this important question of RD can restore AI.

RD is associated with reduced NSTEMI and cardiovascular death in patients with HHD

Prospective randomised studies on the effect of RD on CAD have not been published before. Although the current study was not powered to show a reduction in myocardial infarction or

cardiovascular death, there were non-significant signals that the relative risks of these events may be reduced after RD.

Several mechanisms may explain this novel and unexpected finding of NSTEMI risk reduction. Atherosclerotic plaque rupture is central to the development of ACS. It is well-known that increased inflammation and a thin fibrous cap covering the atheroma increase the risk of plaque rupture and intravascular thrombosis. IST, which is characterised by reduced heart rate variability, is associated with increased levels of interleukin-6 and C-reactive protein (CRP).[116] These mediators may trigger the release of metallo-proteinases from neutrophils which degrade the fibrous atheroma cap. IST also is associated with an increased thrombotic risk. The mediators of the stress reaction can directly affect platelets and the coagulation cascade.[117] Reduced sympathetic tone may, therefore, reduce these pro-inflammatory processes which could potentially promote atherosclerotic plaque stabilisation. Similarly, statins reduce not only LDL-cholesterol and therefore plaque volume, but also high-sensitivity CRP.[118] In our high-risk population, where more than 80% of the patients took statins for secondary prevention, NSTEMI relative risk was further reduced, albeit non-significantly, when RD was added to these preventative therapies. The large difference in NSTEMI is also most likely a play of chance due to small numbers, although it is reasonable to make the observation. To this point, the pathophysiology of the reduction in NSTEMI by RD remains speculative, and this signal needs to be explored in larger, prospective trials.

The finding that RD was associated with reduced cardiovascular death in patients with HHD is novel. Although every study subject had a normal ejection fraction at baseline, the study population had increased cardiovascular risk with established CAD, previous myocardial

infarctions and LVH. These risk factors, coupled with ageing, may synergistically act to increase cardiovascular mortality. The reduced mortality signal with RD is encouraging, but the study was underpowered to detect a possible mortality benefit with RD, which should be assessed in larger high-risk populations.

Office/Ambulatory blood pressure: baseline vs six months follow-up

Similar to Symplicity HTN-3, this study could not demonstrate a superior office blood pressure-lowering effect with RD treatment over sham therapy. A similar effect was demonstrated when comparing 24hr ABPM between groups. Although the sample size was almost seven times smaller than HTN-3 (80 vs 535 study subjects), similar confounders may have influenced the blood pressure results.

Adherence to blood pressure lowering therapy may have influenced the results[119], but randomisation of study subjects should have reduced this confounder. The fact that patients only received light sedation during RD and could still experience RD-associated back and loin pain may have "unblinded" them and could have resulted in them cutting down or skipping their medication. Conversely, increased adherence in the sham group, on the other side, especially if study participants are told that their blood pressure is high by their general practitioners, may explain the drop in their 6MFU blood pressure. Although patients were encouraged to take their medication as prescribed, pill counts were not performed, and anti-hypertensive drug therapy levels in urine or the serum were not checked.

Finally, more recent BP-lowering trials have confirmed a significant, albeit smaller blood pressure-lowering effect with RD in randomised controlled trials. [96-98] A recent meta-analysis

of 12 RCT's and > 1500 patients indicated that RD was associated with a significantly greater reduction of 24-hour ambulatory SBP and office SBP.[120] Furthermore, RD was not associated with an increased risk of major adverse events supporting the notion that percutaneous RD is a safe procedure in the hands of experienced proceduralists.

Echocardiographic parameters that may be influenced by RD

Although the study sample was not powered to show significant echocardiographic changes, RD treatment was non-significantly associated with an increase in LVEF and a reduction in LA diameter. A reduction in LA size may lower left atrial pressure which associates with less stretch forces on the pulmonary venous ostia. Although E/e', a non-invasive marker of diastolic dysfunction, was reduced in both study groups, RD did not lower E/e' more than the sham procedure. The observation that sham-group LV mass was heavier at baseline may have influenced mortality outcomes[121], although LV mass did decrease in the sham group at 6MFU. Unlike previous non-randomised trials, the study could not demonstrate significant regression of LVH at 6MFU in patients treated with RD. More extensive randomised studies are needed to explore if RD can regress HHD and improve diastolic dysfunction. If positive, such a finding may be useful in the management of heart failure with a normal ejection fraction.

RD treatment and supra-ventricular ectopic burden

RD showed a statistical trend towards a reduction of SVES. Conversely, SVES increased with the sham procedure. An underpowered sample size limits further clinical extrapolation. This finding does, however, support the reported association between supra-ventricular ectopy, stroke risk and incident AF.[122]

RD treatment and prolonged ventricular repolarisation

The finding that RD was not associated with QTc-prolongation is reassuring. Conversely, RD was associated with non-significant QTc-shortening which may have beneficial effects on the management of malignant cardiac arrhythmias, e.g. polymorphic ventricular tachycardia. It is well known that left cardiac sympathectomy is protective in patients with LQTS.[123] In a recent meta-analysis, Zhang, et al. found that AF risk increases with 17% for every 10 ms prolongation in QTc.[124] This finding supports current thinking that neural mechanisms modify the arrhythmia risk in LQTS.[65] RD treatment may potentially be useful to treat symptomatic long QT syndrome patients, or those suffering from recurrent implantable cardioverter-defibrillator shocks or those with ablation-refractory ventricular tachycardia.[125]

Usefulness/role of RD in future daily clinical practice

RD-therapy is not ready for everyday clinical practice yet. The final blood-pressure lowering trial is eagerly awaited, but needs careful planning, circumferential ablation catheters and experienced operators to perform the procedure. The technique of RD is not difficult to perform and keen learners should be able to perform the procedure themselves after observing at least three cases. Left radial access avoids complicated groin punctures and subsequent bleeding complications. Unfortunately, the high cost of the catheters (R60,000/catheter) limits its use to the private sector.

The next step to elucidate a potential anti-fibrillatory effect might be to ascertain the incidence of new-onset AF in the original SYMPLICITY HTN-3 population. Similarly, one could also look at our secondary endpoints of myocardial infarction and cardiovascular death. Similar findings may help in the design of future trials.

STUDY LIMITATIONS

Similar confounders in Symplicity HTN-3 may have influenced the blood pressure results of this study. Patients who are significantly hypertensive on at least three antihypertensive drugs are usually shown to be non-adherent to some extent. In this regard, **drug adherence** was not formally assessed.

In regard to the secondary endpoints, namely measurements of autonomic tone, the **small sample size is diluted further by patients who did not return for the peak testing.** Accordingly, it could not be clearly demonstrated that RD treatment is associated with **restoration of autonomic imbalance**. Larger randomised studies that focus on the time and frequency domain analysis of heart rate variability should test this hypothesis.

LV mass differences may have influenced the primary endpoint outcomes, but these differences showed only a statistical trend at baseline. Adjusted risk ratios may help to reduce this possible confounder. Importantly, left atrial size, which is a better predictor of AF than LVH, did not differ between groups at baseline.

Rare safety events may not have been detected. Blinding of the study subjects was not formally assessed but may be less relevant, as the primary endpoint was patient-independent.

Finally, it is not known how long the anti-fibrillatory effect will last since **renal sympathetic nerve regrowth** remains a possibility. Follow-up of patients in this study continues although most of the participants (>80%) have already passed the 3-year mark.

CONCLUSION

The current study shows that renal denervation prevents subclinical atrial fibrillation and reduces fast atrial fibrillation incidence in patients with hypertensive heart disease. These salutary effects of the RD on atrial fibrillation are unique observations which have not been appreciated previously.

Similar to Symplicity HTN-3, superior blood pressure lowering with renal denervation compared to a sham procedure could not be demonstrated. Although similar confounders may have influenced the blood pressure results the exact mechanism(s) by which renal denervation reduces atrial fibrillation in patients with hypertensive heart disease may, therefore, occur independently of blood pressure lowering.

Although heart rate profiles at rest, during ambulation and after exercise improved non-significantly with RD, the study could not demonstrate restoration of autonomic imbalance. RD treatment was associated with a reduced NSTEMI incidence and reduced cardiovascular death in patients with HHD. More extensive multi-centre prospective trials should test these hypotheses by assessing direct sympathetic nerve effects and vascular inflammatory markers.

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CHAPTER 5

ADDENDUM

First reported cases: renal denervation with second-generation multi-electrode catheter via brachial and radial access

MJ Heradien, J Augustyn, A Saaiman, PA Brink

Abstract

Renal denervation is a minimally invasive procedure that aims to reduce brain–kidney sympathetic cross-talk. Despite the negative results of the recent SYMPLICITY HTN-3 trial, the procedure is considered safe and has been associated with many beneficial effects, including the reversal of hypertensive heart disease substrate and the prevention of cardiac arrhythmia. The first-generation radiofrequency catheter system featured a monopolar catheter that required sequential single-point energy application, followed by rotation, partial withdrawal of the catheter and re-application of energy. The latest generation device features four electrodes configured in a helical arrangement that can simultaneously ablate in four quadrants of the vessel circumference. Renal denervation via brachial or radial arterial access with the second-generation system has not been described before.

Keywords: hypertension, renal denervation, atrial fibrillation

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Renal denervation (RD) is a minimally invasive procedure that aims to reduce brain–kidney sympathetic cross-talk. Despite the negative results of the recent SYMPLICITY HTN-3 trial,[1] the procedure is considered safe and has been associated with many beneficial effects, including the reversal of hypertensive heart disease substrate and the prevention of cardiac arrhythmia.[2]

The first-generation radiofrequency (RF) catheter system featured a monopolar catheter that required sequential single-point energy application, followed by rotation, partial withdrawal of the catheter and re-application of energy. The latest generation device features four electrodes configured in a helical arrangement that can simultaneously ablate in four quadrants of the vessel circumference (Fig. 1A). Although the system is designed for femoral access, brachial or radial procedural access has possible advantages, including reduced risk of bleeding and easier access to the renal arteries due to the acute take-off angles of the renal artery from the abdominal aorta.

As part of our ongoing trial aiming to determine whether sympathetic modulation with RD can prevent recurrence of atrial fibrillation ('RDPAF'; clinicaltrials.gov identifier: NCT01990911), we report on two cases of RD with the next generation RD catheter system performed via brachial or radial access. The trial was approved by our local ethics committee, conformed to the Declaration of Helsinki, and the subjects provided written informed consent.

Case 1: renal denervation via brachial arterial access

Our first case was a 62-year-old female patient (body mass index > 30 kg/m^2) with a history of uncontrolled hypertension and type 2 diabetes mellitus, and paroxysmal atrial fibrillation managed with rivaroxaban, which was discontinued four days prior to the procedure. Baseline office blood pressure was 150/90 mmHg.

Routine femoral access was achieved. However, catheter access to the right renal artery failed due to the acute anatomical take-off of the vessel. Therefore, it was decided to attempt access via a brachial approach as an alternative. Percutaneous left brachial arterial access was achieved with a 6-Fr introducer sheath (Terumo), 6-Fr multipurpose guiding catheter (Medtronic) and a 190-cm, 0.014-inch gage BMW™ guide wire (Abbott Vascular). A Symplicity Spyral™ (Medtronic) catheter was then introduced over the guidewire, after removing the straightening tool, resulting in approximately 125 cm of catheter length (Fig. 1B).

The diameter of the main renal artery was approximately 6.5 and 5.5 mm on the left and right side, respectively. Access to both arteries was readily attained, and 17 and 13 lesions were created in the right and left renal arteries, respectively (Fig. 2).

Fig. 1A. Symplicity Spyral® renal ablation catheter is an over-the-wire system that enables simultaneous quadripolar renal artery ablation.

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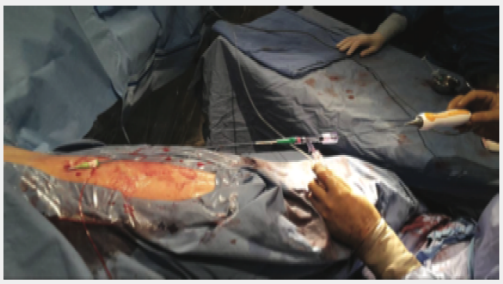


Fig. 1B. Symplicity Spyral® catheter threaded through the multipurpose guiding catheter with right brachial access point.

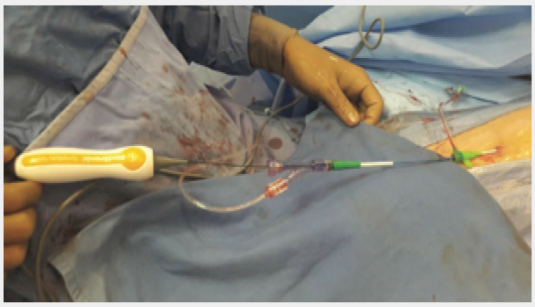


Fig. 3. Left radial access: note how much of the catheter is still outside the patient.

Case 2: renal denervation via radial arterial access

The second case was performed on a 63-year-old male with a history of syncope, obstructive sleep apnoea, hypertension and baseline blood pressure of 160/100 mmHg. Percutaneous left radial arterial access was achieved with a 6-Fr introducer sheath (Terumo), 6-Fr multipurpose guiding catheter (Medtronic) and a 190-cm, 0.014-inch gage Thunder™ guide wire (Medtronic). The Spyral catheter was then introduced over the guidewire, after removing the straightening tool, resulting in approximately 125 cm of catheter length (Fig. 3).

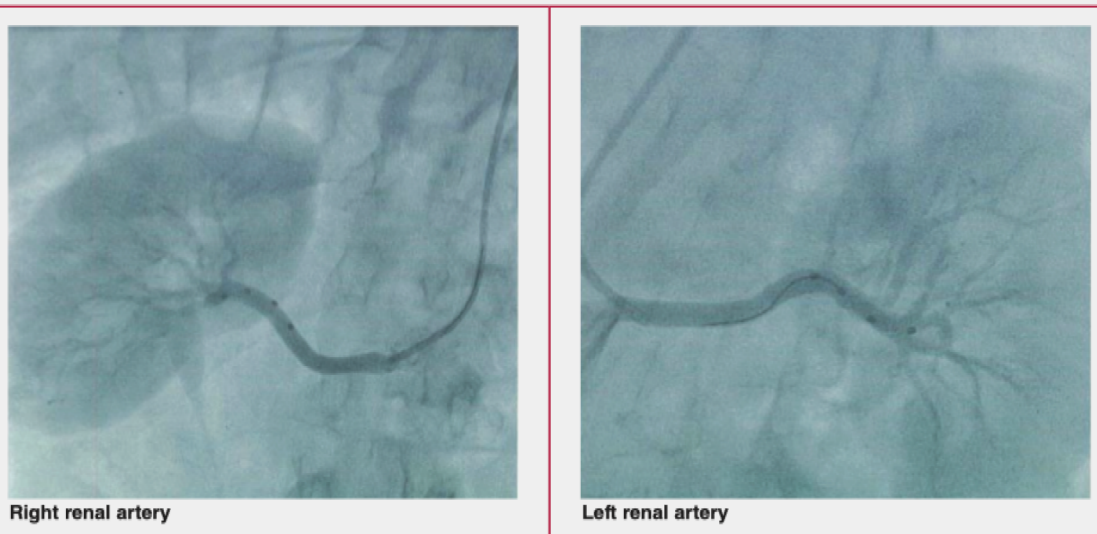
The diameter of the main renal artery was approximately 7 and 6 mm on the left and right side, respectively. Adequate catheter access to the renal arteries was attained and 24 and 20 lesions were performed in the right and left renal arteries, respectively.

For both cases electrode temperature, impedance and impedance decreases were in the typical range for all lesions. Typical generator codes indicating sub-optimal electrode contact were occasionally observed and were addressed during the procedure by successful repeated energy delivery to the specific electrodes. No procedural complications occurred, and the arterial access site was managed post procedurally with routine manual compression.

The patients were discharged the same day as the procedure, and no further complications have been reported to date. Both patients will continue to be monitored according to the clinical protocol (Table 1).

Discussion

To our knowledge, these are the first reported cases of RD through brachial and left radial access, respectively, using the second-generation multi-electrode RF generation system. Previous case reports have described successful RD via brachial access with the first-generation monopolar system.[3,4] Compared to the traditional femoral approach, trans-radial or brachial percutaneous procedures for coronary interventions generally have a lower risk of bleeding complications, fewer access site



Right renal artery

Left renal artery

Fig. 2. Bilateral renal artery denervation was successfully performed.

Table 1. Comparison: baseline versus follow up after renal denervation (RDN)

	Before RDN (baseline)	*Follow up*	*Reduction*
Patient 1: right brachial approach Office BP (mmHg)	05/02/2015: 159/94	12/06/2015: 137/77	22/17 mmHg
ABPM: mean BP (mmHg)	137.1/78.1	130.2/74.9 (4 months after RDN)	6.9/3.2 mmHg
BP meds (3 drugs)	Prexum Plus/ Bisocor	Prexum Plus/ Bisocor	no
Patient 2: left radial approach Office BP (mmHg)	23/06/2015: 173/94	17/08/2015: 128/73	45/21 mmHg
ABPM: mean BP (mmHg)	155.5/85	133.2/82 (4 months after RDN)	22.3/3 mmHg
BP meds (4 drugs)	Co-Pritor/Bisocor/Spiractin	Co-Pritor/Bisocor/Spiractin	no

complications and lower hospital costs, and are preferred by patients. Likewise, the unique geometric anatomy of the renal arteries relative to the abdominal aorta may make renal artery access easier from this superior approach.

The Symplycity Spyral catheter measures 117 cm from spiral tip to shaft end, however, we found that removal of the attached 'straightening sheath', increased the usable length to 125 cm, which was adequate for these cases. Both cases had encouraging outcomes with no adverse events. During both procedures, we intentionally targeted the distal portion of the main vessel as well as the distal renal artery beyond the main bifurcation because the sympathetic nerves have been shown to be closer to the arterial lumen in these regions.'

Note that the patients described here did not have so called 'treatment-resistant' hypertension. However, these subjects received RD therapy as part of a separate clinical trial testing the hypothesis that RD therapy may reduce recurrence of atrial fibrillation. Also, note that the system used in these cases was designed specifically for femoral procedural access and this is specified clearly in the product labelling. However, we chose to apply this device in an 'off-label' fashion in order to determine the potential to improve the procedural safety and outcome.

Conclusion

We demonstrated that RD therapy is feasible with the currently approved multi-electrode RF system with either brachial or radial access, although larger prospective studies are required to determine the actual safety and efficacy of this alternative. Such an approach could perhaps reduce the rate of vascular complications associated with femoral access and also allows for same-day discharge. Finally, we suggest that future generations of RD catheter systems be designed with the goal to allow for brachial and radial arterial access.

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Review Article

Renal denervation: dark past, bright future?

Marshall Heradien, Felix Mahfoud, Doug Hettrick, Paul Brink

Abstract

The purpose of this review is to update the reader on the relevance of autonomic nervous system imbalance in clinical cardiology. Increased sympathetic tone associates with the metabolic syndrome, hypertension and cardiac arrhythmias. With the kidneys playing a pivotal role in increased peripheral resistance, sodium and water retention and other mechanisms, renal denervation (RD) may theoretically restore autonomic imbalance and improve cardiovascular outcomes. Landmark RD trials and novel uses for RD in cardiac arrhythmia management are discussed.

Keywords: autonomic imbalance, hypertension, hypertensive heart disease, atrial fibrillation, renal denervation

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What is autonomic imbalance?

The autonomic nervous system consists of a sympathetic and parasympathetic system. Autonomic imbalance (AI) defines a state of relatively increased sympathetic tone (IST) and/or decreased parasympathetic tone. AI is associated with many disease components including heart failure, atrial fibrillation, obesity and chronic kidney disease.[1-4] Our modern lifestyle of high stress levels, reduced exercise and poor diets rich in salt and carbohydrates undoubtedly fuels both the metabolic syndrome and AI.

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AI and sudden cardiac death

Interestingly, AI is also associated with sudden cardiac death (SCD) during severe emotional stress.[5] Congenital long-QT syndrome also illustrates this association particularly well.[6] Symptomatic mutation carriers typically experience syncope and sometimes SCD during situations associated with IST, such as excitement, swimming or exercise. Conversely, higher resting vagal tone seems to be protective, and anti-sympathetic therapy such as beta-blockers or left cardiac sympathetic denervation (LCSD) are established therapies for this inherited cardiac ion channelopathy.

Another example where AI was associated with and even predicted SCD, came from a prospective cohort of apparently healthy young male French civil servants.[7] Here, Jouven and co-workers used exercise-related heart rate profiles as surrogate markers of cardio-autonomic tone. They found that faster resting heart rate (> 75 bpm), indicative of IST, and slower post-exercise recovery of heart rate (< 25 bpm), indicating reduced parasympathetic tone, were associated with a significantly higher SCD risk later in life.

The kidneys play a central role in autonomic dysfunction

With the kidneys playing a pivotal role in increased peripheral resistance, sodium and water retention and other mechanisms, renal denervation (RD) may theoretically restore autonomic imbalance and improve cardiovascular outcomes.[8] Innovative endovascular techniques provide minimally invasive access to reduce sympathetic brain–kidney cross-talk, which may restore AI and prevent its associated complications.

Renal nerve supply: anatomy and physiology

Anatomical and physiological knowledge of the renal nerve supply supports the hypothesis that RD should lower blood pressure and consequently produce beneficial cardiac effects.[9] The afferent sympathetic renal nerves, mostly located in the renal pelvis, transmit signals via the dorsal spinal cord to the brain when activated by stretch forces (Fig. 1). Activated centres in the brain include the nucleus tractus solitarius, medulla oblongata and paraventricular hypothalamic nuclei. These signals increase vasopressin and oxytocin release, accompanied by increased activation of efferent sympathetic neurons. These neurons run along paravertebral ganglia and large blood vessels, where they exit to vital organs located in the thoraco-lumbar region. In the thorax, sympathetic nerves terminate in the sino-atrial node, atrio-ventricular node and ventricles. Here, sympathetic stimulation increases chronotropy, dromotropy and inotropy,

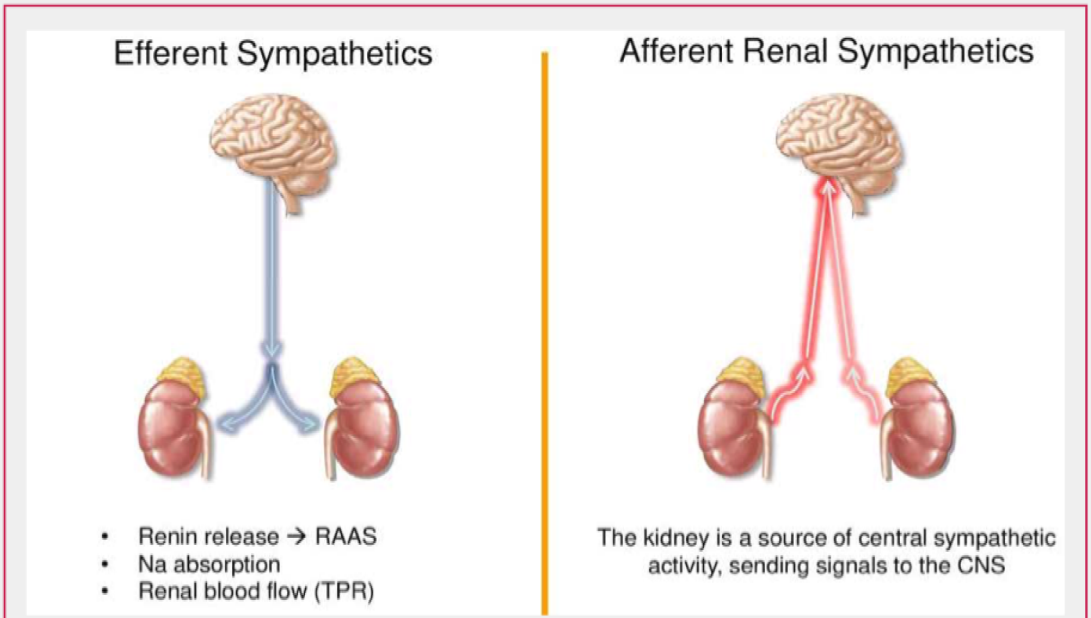

Fig. 1. Renal sympathetic nerves facilitate brain–kidney cross-talk and play a central role in BP control and regulation of autonomic tone (supplied by Medtronic, Inc).

respectively. Cumulatively, these effects increase cardiac output and systolic blood pressure.

In the lumbar region, the efferent sympathetic nerves enter the kidneys via the renal arteries. They arborise alongside the renal artery, running in the vasa vasorum and terminate in the efferent glomerular arteriole (EGA), juxta-glomerular apparatus (JGA) and renal tubules. JGA activation results in renin release, which activates the renin–angiotensin–aldosterone system (RAAS). End-products of RAAS activation, angiotensin II (AT-II) and aldosterone induce vasoconstriction and tubular sodium and water retention, respectively. AT-II constricts the EGA, which raises intra-glomerular pressure and filtration rate. AT-II also increases peripheral resistance, which increases diastolic blood pressure, cardiac afterload and coronary perfusion.

It is almost incomprehensible that mere stretching of the renal pelvis by increased urine production would produce such a cascade of events that result in increased cardiac output, augmented glomerular filtration and subsequent adrenal activation. The primary renal aim would be to restore water and sodium balance acutely. Chronic and inappropriate activation of this system results in hypertension and its sequelae. Although IST is not the only cause of essential hypertension, there is strong evidence that the autonomic nervous system plays a critical role in hypertension pathogenesis and endothelial health.[10,11]

Hypertensive heart disease and cardiac arrhythmia

Uncontrolled hypertension often results in hypertensive heart disease (HTHD), which provides an ideal arrhythmic substrate.[12] Interstitial cardiac fibrosis, promoted by aldosterone secretion, fractionates the depolarising electrical wave front. Left ventricular hypertrophy (LVH) associates with increased myocardial oxygen consumption, and in the presence of concomitant coronary atherosclerosis, the endocardium remains at an increased risk of hypo-perfusion and myocardial death. Often, coronary plaques rupture because of a sudden surge in blood pressure or increased intra-plaque inflammation. IST has been shown to associate with both precipitants.[13] Additionally, in patients with obstructive sleep apnoea, sympathetic surges followed by intense vagal reflexes have been shown to precipitate paroxysmal atrial fibrillation (AF) and associate with nocturnal SCD.[14]

Renal denervation to modulate autonomic activity: human proof-of-principle studies

The hypothesis that denervation of the renal sympathetic nerves should result in blood pressure reduction was successfully tested in clinical trials. In humans, non-selective surgical splanchnicectomy, which includes RD, was frequently performed as primary hypertension (HT) treatment,[15] but common side effects, such as impotence, orthostatic hypotension and incontinence, led to its disappearance from current-day practice. This led to the concept that the efferent nerves in the renal artery adventitia might yield an easily accessible target. The advent of endovascular therapy made access to the renal arteries possible through femoral artery puncture (Fig. 2). Heradien *et al.* recently reported that RD could also be performed via brachial or radial artery puncture.[16] This unique form of RD vascular access eliminates the risk of groin-related hypertensive arterial bleeding and allows same-day hospital discharge.

Fig. 2. Renal denervation is accomplished with a quadripolar radiofrequency catheter via arterial puncture. The catheter is advanced over a guidewire into the distal renal artery, the wire is removed and the catheter conforms in a spiral form to make close contact with the vessel wall. Radiofrequency heat energy is then delivered in an attempt to destroy the efferent renal nerves in the vasa vasorum (copyright for figure obtained from Medtronic, Inc).

Landmark RD trials

The landmark endovascular RD trials are often colloquially referred to as the Symplicity HTN Trilogy. The first trial that kindled interest was published a decade ago. SYMPLICITY HTN-1 was a multicentre, non-randomised, safety and proof-of-principle cohort study.[17] Patients with so-called resistant HT, defined as an office blood pressure (BP) ≥ 160/90 mmHg on three drugs, including a diuretic, underwent bilateral RD.[17] Compared to baseline, follow-up office BP was dramatically reduced and the scientific world was sensitised that RD might offer a potential cure for the proverbial 'silent killer'.[18]

SYMPLICITY HTN-2 was the first randomised, controlled trial (RCT) that tested the hypothesis that RD was superior to medical therapy in the management of resistant HT.[19] Again, similarly to SYMPLICITY HTN-1, office systolic BP was reduced with RD by 32 mmHg at the six-month follow up. This trial resulted in an all-time high interest and a flickering hope that RD might add an important new weapon in the fight against HT. Whereas the procedure was registered for use in European countries, the Food and Drug Administration insisted on a further trial before registration in the USA; hence, the SYMPLICITY HTN-3 trial was designed.[20]

SYMPLICITY HTN-3 randomised 535 treatment-resistant hypertensive patients to RD or sham RD. The results were interesting but unexpectedly disappointing. Although both groups had significant office BP reductions at the six-month follow up, RD did not meet the primary efficacy endpoint of the mean difference between groups of 5-mmHg reduction in office systolic blood pressure (SBP). These surprising results brought the 'speeding RD train to a grinding halt'.[21] However, several confounders have been identified that may have contributed to the failure of SYMPLICITY HTN-3.[22]

Despite rigorous trial design and execution, several unaccounted for factors may have contributed to the failure of SYMPLICITY HTN-3 to demonstrate RD efficacy relative to the sham control.[23] These include patient demographics, medication adherence, the Hawthorne effect, the placebo effect, trial conduct, regression to the mean, operator experience and catheter design.

Patient demographics: Unlike previous SYMPLICITY trials, SYMPLICITY HTN-3 also recruited African-American (AA) patients (26% of the prospective cohort). Compared to the non-AA sub-group, AA patients in the sham group had a 9.2-mmHg greater decline in office SBP at six months. This change in sham office SBP was nearly twice as large in AA as non-AA patients. In a *post hoc* analysis, the authors concluded that this unexpected BP reduction in a sham group was likely due to increased post-randomisation medication adherence and that the change after renal denervation was probably not confounded by race.[24]

Although this exploratory report does not provide definitive evidence that the SBP response to RDN differed by race, it is generally accepted that hypertensive patients of African ancestry are poor responders to angiotensin converting enzyme (ACE) inhibitor and beta-blocker therapy.[25] This dogma was recently challenged in the Creole study where investigators found that black Africans responded better to perindopril–amlodipine than to perindopril–thiazide combination therapy.[26] Despite these encouraging results that black Africans may respond to ACE inhibitor therapy, it remains to be proven that blacks are poor RD responders.

In the current South African environment, however, racial confounding in science led to the retraction of a controversial article that was recently published.[27] Unfortunate events like these may hamper expedient ethical approval of BP studies investigating different racial responses to antihypertensive treatment.

Many have hypothesised that the beneficial effects of RD may be attenuated in patients with later-stage peripheral artery disease or increased vascular stiffness, which might limit the capacity for reverse vascular remodelling following the procedure. Indeed, several reports indicate that various indices of increased arterial stiffness predict improved BP response following RD.[28-31] Likewise, Mahfoud and colleagues showed in two separate retrospective analyses that patients with isolated systolic hypertension, a course but easily determined identifier of increased arterial stiffness (defined as office SBP > 140 mmHg and DBP < 90 mmHg), had more significant BP drops than patients with combined systolic and diastolic hypertension.[32] For this reason, patients with isolated systolic hypertension were explicitly excluded from the sham controlled RCTs that followed SYMPLICITY HTN-3.

<3rd level head>*Medication adherence:* Although patients were encouraged to continue taking their prescribed medication diligently throughout follow up, urine or blood levels of antihypertensive drugs were not measured. Surprisingly, about 40% of the patients changed their antihypertensive medication regime after randomisation. Furthermore, recent evidence from multiple hypertension trials, including RDN trials, clearly indicates that non-adherence to prescribed medications is common, perhaps greater than 50%, and may vary within patients even during the clinical trial follow-up period.[33]

Such rampant non-adherence may be due to multiple factors, including lack of understanding of the risks and benefits

of hypertension therapy, socio-economic factors limiting drug access, social support, depression and anxiety, regimen complexity and side effects. Taken in context with the significant drop in BP in the sham group, it is reasonable to suspect that unpredictable variable adherence to antihypertensive medication may have impacted on the results of SYMPLICITY HTN-3. This concern led to the design of 'off-medication' trial designs following SYMPLICITY HTN-3. These are discussed below.

Hawthorne effect: This effect describes the adjusted behaviour of trial participants to seemingly please/impress study investigators.[34] Examples of such behaviour include patients taking their medication more diligently, reducing their salt intake and exercising more regularly. It is difficult, if not impossible, to reduce this type of behaviour.

Regression to the mean (RTM): RTM is defined as the tendency for an extreme measurement on one occasion to become less extreme when measured again. This may explain why, unlike previous SYMPLICITY trials, SYMPLICITY HTN-3 showed only a –4.1-mmHg between-group SBP treatment difference. To reduce this niggly statistical phenomenon, statisticians recommended that, rather than a Student's *t*-test, analysis of covariance (ANCOVA) might be a more appropriate test to use in future RDN trials.[35]

Finally, it is essential to note that the potential biases introduced by both the Hawthorne effect and regression to the mean can be addressed by randomisation.

Operator experience and catheter design: In SYMPLICITY HTN-3, 112 operators performed an average of 3.3 procedures per operator.[20] Less than five procedures were performed per site, and more than 50% of the operators performed two or fewer procedures in the trial. Several technical challenges may face the inexperienced operator: difficult intubation with poor guide catheter back-up, accessory polar renal arteries (smaller than the main vessel) that could not be treated, the 'hostile' groin, e.g. morbid obesity and inability to visualise anatomically whether a successful four-quadrant ablation was performed, using a two-dimensional fluoroscopic image. Operators were also instructed to avoid distal renal arteries, but Sakakura *et al.* subsequently discovered that in human cadavers, the renal nerves run closer to the arterial lumen distal to the renal bifurcation than proximally (2.6 mm vs 3.4 mm).[36] These sites, although being typical 'sweet spot targets' for denervation, were therefore missed in most cases. Animal studies have shown that RDN success is very much dependent on distal denervation.[37,38]

The Flex catheter (Medtronic Inc) is a single-point denervation system that uses a proprietary algorithm of retraction, flexion and rotation to focus radiofrequency energy points in recommended anatomical sites of the renal artery. It was challenging to perform enough four-quadrant ablations with the old system but the newer Symplicity Spyral catheter, which is an over-the-wire system, is a safer, more intuitive system that not only associates with more four-quadrant ablations but also enables the operator to safely perform distal ablations without the danger of perforation or dissection. The newer system typically requires less fluoroscopy time with less ionising radiation and lower doses of iodine contrast agent, resulting in better renal function outcomes post-procedurally.

A new generation of sham, controlled RCTs

Recently reported positive results from three new randomised sham, controlled trials might have rekindled interest in RD. All three trials were designed to compensate for the confounding factors identified in SYMPLICITY HTN-3. Although smaller in scope than SYMPLICITY HTN-3, the sham controlled SPYRAL HTN OFF-MED trial tested the hypothesis that RD would reduce BP in the absence of antihypertensive drugs.[39] Patients with milder HT were asked to discontinue their BP medication for at least one month before and during the trial duration. Similar to SYMPLICITY HTN-3, patients were randomised to RD or sham RD. Compliance was checked with urine drug levels throughout the trial. RD was performed by experienced proceduralists, who also denervated the distal renal arteries with a second-generation quadripolar catheter (Symplicity Spyral).

Results were reported at three months and albeit much less than previous trials, showed that RD reduced office and ambulatory BP in hypertensive drug-naïve patients, confirming the proof of concept. Likewise, the sham, controlled SPYRAL HTN ON-MED trial showed similar, if not greater improvements in both office and 24-hour blood pressure six months post-RD in a similar population treated with one to three antihypertensive agents.[40]

Finally, the sham, controlled RADIANCE HTN SOLO trial employed a design quite similar to SPYRAL HTN OFF-MED but using an ultrasound-based catheter denervation system (Otsuka/ReCor Paradise).[41] Interestingly this catheter was not advanced into the distal renal arteries but only into the main vessel. The results after two months showed significant reductions in office and ambulatory BP comparable to the SPYRAL HTN trials.

Together, these trials blew new life into endovascular RD and provided the much-needed hope that RD does indeed lower BP in selected patients when the right technique is used by experienced renal denervationists. Now the world waits with bated breath for the final RD trial that will use the knowledge learned from hard lessons, and hopefully either bury or enthrone RD in its rightful place in HT management.

Types of patients likely to benefit from RD

Three types of patients will likely benefit from RD. The first and most prevalent group are those who are non-adherent to their antihypertensive therapies (AHT). Almost one-third of all hypertensive patients never start with their prescription of antihypertensive drugs when first diagnosed.[42] The variable plasma half-life of AHT also explains why some AHT lack true 24-hour cover and why uncontrolled hypertensive patients experience most of their events during the early morning hours when drug levels reach their nadir. The 'always-on effect' of RD may help to reduce these pharmacological shortcomings.

The second group that may also benefit are those patients with clinical signs of IST, for example a resting heart rate of ≥ 75 bpm in beta-blocker-naïve subjects, patients with non-dipping or during 24-hour ABPM.[7,43] The dipping of blood pressure at night is mediated by reduction of daytime sympathetic tone and increase in nocturnal vagal tone. Finally, the group that will probably benefit most are patients with the metabolic syndrome.[44]

Shortcomings of RD treatment for HT

These can be divided into two subgroups: technical challenges, and patients who will show an inadequate response to RD. The first shortcoming of current RD treatment is that the completeness of RD cannot be accurately assessed. The operator, therefore, has no indication if he has successfully denervated the kidney. Second, since patients with polar renal arteries and challenging renal artery anatomy (aneurysms, renal artery stenosis and calcification) were excluded from trials, there are no data on whether these subgroups will respond to RD. Patients with isolated systolic hypertension will also show less response to RD.[45] RD has not been tested in patients with secondary HT, but it could theoretically reduce BP in patients with inoperable paragangliomas, since RD reduces circulating catecholamine levels.[46] Finally, although RD probably reduces BP, if correctly performed, patients should continue to take their BP medication.

Can future studies address current uncertainties in RD?

Future studies should include an objective method to assess the completeness of RD during the procedure. Non-adherence to AHT and RTM phenomena confound RCTs. These challenges can be reduced by combination AHT (reduced pill burden) and advanced statistical tests.

AF: current management and iatrogenic side effects

Paroxysmal AF, which is a common complication of uncontrolled HT and HTHD, originates from the muscular sleeves inside the pulmonary veins where they enter the left atrium.[47] Current rhythm-control treatment of paroxysmal AF can be accomplished through drugs or pulmonary venous isolation (PVI) techniques. Drug treatment with amiodarone is often life-long, which associates with dangerous side effects, including thyroid dysfunction, corneal deposits, hepatic enzyme abnormalities and irreversible lung fibrosis.

PVI, on the other hand, is performed under general anaesthesia with either hot or cold ablation in an attempt to electrically isolate the pulmonary veins from the left atrium. Hot ablation uses radiofrequency (heat) energy to induce scar tissue around the pulmonary venous ostia. Cold ablation uses liquid nitrogen to freeze the pulmonary venous–atrial junctions. A high cure rate can be achieved with these techniques that require atrial trans-septal puncture. The Fire and Ice trial confirmed that cold ablation is non-inferior to hot ablation.[48] Despite these technological advances, PVI is associated with rare but dangerous side effects, including cardiac perforation, tamponade, phrenic nerve palsy and fatal atrio-oesophageal fistula.

Can RD treat paroxysmal AF?

RD, which has an excellent safety profile, may improve outcomes of catheter ablation in hypertensive patients with AF.[49] Canine studies suggest that RD induced morpho-electrophysiological changes that reduced the AF substrate.[50,51] These include changes in the atrial effective refractory period, P-wave duration, AF cycle length and reduced atrial fibrosis regarding substrate modification. Meta-analyses of human studies have shown that RD was associated with regression of both LVH and left atrial hypertrophy.[52]

Pokushalov and colleagues have also shown in an RCT that RD, when coupled with pulmonary venous isolation as paroxysmal AF treatment, significantly reduced incidental AF during follow up.[53] The trial was criticised for its small sample size and the lack of AF monitoring with an implantable loop recorder. Another small non-randomised trial has shown evidence that RD alone may reduce AF triggers and AF burden in patients with both HT and paroxysmal or persistent AF.[54] Results of a larger prospective trial where RD was used as stand-alone, upstream therapy to prevent AF in patients with HTHD are currently awaited (NCT01990911).[55]

Conclusion

AI plays a vital role in many prevalent cardiac diseases. Restoration of AI provides the promise of upstream modification and prevention of these disease complications. With the kidneys at the proverbial eye of the hypertensive cyclonic storm, RD may provide an alternative treatment for HT and many of its notorious complications, including paroxysmal AF. Results of prospective, randomised, sham, controlled trials are eagerly awaited.

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Renal denervation in South Africa

To the Editor: Renal denervation (RD) is a minimally invasive therapy aimed primarily at hypertension.[1] The procedure involves modification of the renal sympathetic nerve supply, which courses around the renal arteries. Access to the renal arteries is obtained via peripheral vessels (femoral, radial or brachial artery), and radiofrequency energy is applied to the arterial wall.[2] After proof-of-concept studies in animals and humans, the SYMPLICITY HTN-2 trial demonstrated a significant blood pressure reduction in patients with resistant hypertension, compared with pharmacological management.[3] Surprisingly, RD was not found to be more effective than a sham procedure for resistant hypertension in the SYMPLICITY HTN-3 trial.[4] This trial, however, was subject to significant limitations, including the inability to monitor treatment adherence and changes of pharmacotherapy during the trial, as well as variation in the extent of RD performed in individual patients. Three sham-controlled trials have been published since, addressing many of the shortcomings of SYMPLICITY HTN-3. The SPYRAL-HTN-OFF MED trial[5] was designed to control for differences in between-group pharmacotherapy, and blood pressure at 3 months' follow-up was significantly lower in the RD group than in the sham procedure group. In the SPYRAL-HTN-ON MED trial,[6] pharmacotherapy was continued, and blood pressure control was also improved in RD recipients. In the endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO) trial,[7] RD was more effective in decreasing blood pressure than a sham procedure.

The latter three trials have provided compelling new evidence for RD efficacy, with few major complications. By correcting for the confounders of the SYMPLICITY-HTN-3 trial, the SPYRAL-HTN-OFF MED, SPYRAL HTN-ON MED and RADIANCE-HTN SOLO trials have provided substantial evidence in favour of RD, expanding its scope to patients who do not suffer from resistant hypertension. In preclinical and clinical models, RD has demonstrated benefits beyond blood pressure reduction, e.g. attenuation of adverse left ventricular remodelling and improvement in left ventricular systolic function, which have led to the investigation of RD for applications other than hypertension treatment, e.g. the prevention of atrial fibrillation.[8]

RD has not become widespread as a treatment option for hypertension in South Africa (SA). All RD therapy is currently provided in the private sector. The South African Heart Association and the Southern African Hypertension Society released a consensus statement regarding RD in 2014,[9] which recommends that it only be performed as part of prospective studies or registries. Although these recommendations were written before the SPYRAL-HTN-OFF MED, SPYRAL HTN-ON MED and RADIANCE-HTN SOLO trials were published, they allow for patients with resistant hypertension to be referred to centres of expertise for possible inclusion in a trial or a clinical registry. In a recent study of more than 10 000 individuals in sub-Saharan Africa,[10] SA had the highest prevalence of hypertension, with a high degree of uncontrolled blood pressure (55.4% women, 68.1% men) in the study sites. Given the substantial healthcare burden of hypertension in SA and the latest evidence base, the time has come to review the local recommendations and allow RD technology to penetrate the SA healthcare system. This will only be achieved by a co-ordinated effort between healthcare providers, funders and regulators.

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